EXHIBIT 11

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCT MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***This Document Relates to All Cases***	**Civil Action No. 3:16-md-2738-MAS-RLS** **MDL No. 2738**

SUPPLEMENTAL EXPERT REPORT OF

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Dated: November 15, 2023

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I. INTRODUCTION AND SUMMARY.

I have been asked to supplement my previous expert report submitted on November 16, 2018 on whether the genital use of talcum powder products (i.e., Johnson's Baby Powder and Shower to Shower) are causally related to an increased risk of ovarian cancer. The body of evidence was sufficiently mature and consistent at the time of my initial assessment to conclude that perineal exposure to talcum powder products was *causally* related to an increase in the risk of ovarian cancer. The assessment was based on the totality of the medical and scientific evidence from systematic reviews, pooled analyses and consistent findings of a statistically significantly increased risk in epidemiologic studies,[1] evidence of retrograde migration and inhalation of talc, presence of known or suspected carcinogens in talcum powder products, and inflammatory tissue response that initiates multiple pathways and biological mechanisms by which talcum powder products can cause ovarian cancer. While these factors carried the most weight in my assessment, available data on the biological gradient of talc exposure and ovarian cancer (dose response) also supported my opinion.[1]

New studies when interpreted in the context of the mature evidence base present at the time of initial assessment have reaffirmed my conclusion that the association between genital talcum powder use and the development of ovarian cancer is causal. Several new umbrella reviews,[2] meta-analyses,[3,4] pooled analyses of case control studies,[5-8] and case control studies[9] provide further evidence in support of a statistically significant, precise and consistently increased risk after adjusting for multiple confounders and further support for the viewpoints on ***strength of association*** **and** ***consistency***.[10,11] The magnitude of risk of ovarian cancer among *frequent users* of genital talc (at least two times per week) was noted to be significantly higher **OR 1.47 (95% CI 1.31, 1.65)**[3] than the significantly increased risk seen in previous studies comparing ever uses to never users.[1,11] Health Canada identified that more than 92% of case-control studies have noted a positive association with the overwhelming majority of them being statistically significant.[1,10] Three out of four cohort studies reported a positive association. The results from the new pooled analysis of cohort studies[12] is also consistent with an increased risk, despite significant limitations such as the inability to account for latency effects, their limited statistical power [number of cases of ovarian cancer in the case-control studies (n=13421 cases) is sixfold higher than the pooled cohorts (n=2168)],[1,12] exposure misclassification, and depletion of susceptibles, all of which biased the findings of the cohort studies towards the null. Despite these limitations, the study also noted a significantly increased risk among women with patent reproductive tracts which is ***consistent and coherent*** *with a biologically plausible mechanism* of increased risk mediated via retrograde migration of talc particles.[13,14] There is additional evidence of ***dose response or biological gradient*** between the use of genital talcum powder use and ovarian cancer in new case-control studies[9] and meta-analysis,[11] which add to the weight of evidence from earlier assessments.[1] All epidemiologic studies noted the use of talc prior to development of ovarian cancer establishing **temporality**. The evidence base on ***biological plausibility*** has been strengthened by new studies with evidence on retrograde migration of talc and induction of inflammation, alteration of redox potential.[13-16] Talc alone, and especially in combination with estradiol, introduced changes in gene expression that promotes a pro tumorigenic environment,[17] providing a biologically ***coherent*** explanation of why talc use is associated with an increased risk among pre-menopausal women and post-menopausal women who used hormone therapy.[18] Using a weight of evidence approach Health Canada *confidently* concluded that database is sufficient to conclude that

perineal talc can cause ovarian cancer regardless of the presence of asbestos. [10] The FDA, Johnson & Johnson's testing, and the analyses of Drs. Longo and Rigler have documented the presence of asbestos in talcum powder products, an established cause of ovarian cancer. [19,20,21,22,23] Asbestos is classified as a Class 1 carcinogen along with asbestiform talc.[24,25] In summary, it is my opinion, to a reasonable degree of scientific and medical certainty, that the updated and cumulative body of evidence continues to support and reaffirm my conclusion that talcum powder products can cause ovarian cancer.

II. METHODS FOR SYSTEMATIC SEARCH AND ASSESSMENT OF CUMULATIVE BODY OF EVIDENCE

Systematic Search. I conducted a systematic search of *Scopus and PubMed* on Sep 22, 2023. I restricted the search to peer reviewed articles published between 2017 to date. I also signed up to receive electronic notification of articles from PubMed. I used the following search terms :

Scopus Search Terms : (TITLE-ABS-KEY (talc) AND TITLE-ABS-KEY (ovarian AND cancer)
Pubmed Search Term : ("talc"[MeSH Terms] OR "talc"[All Fields]) AND ("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields])

Eligibility criteria. I included epidemiological studies which provided original data on the association between talc and ovarian cancer. I included study designs including cohort studies and case control studies. I also included umbrella reviews, systematic reviews and meta-analyses and pooled analyses of epidemiological studies. I also examined the references of included studies and cited articles to find additional articles which provided original data. I also included studies that reported on the biological plausible mechanisms and causal pathways that either support or refute the role of talc in the development of ovarian cancer. These could include animal studies, i*nvitro* studies or *in vivo* studies in humans.

After consideration, I excluded narrative reviews or opinion articles that did not provide original data and those that were not deemed relevant to the causal question. I excluded studies of products that reported on exposures other than talc. I excluded studies that did not report on the association between genital exposure to talc such as occupational exposure to talc. I excluded studies that reported outcomes other than the risk of ovarian cancer with genital talc exposure. I also excluded studies that did not report on the biological plausibility of talc and ovarian cancer. Some articles were excluded for fulfilling more than one exclusion criteria.

I reviewed the full text of included manuscripts and provide a summary of their key findings below with attention to their strengths and limitations. Notably, all of these studies were examined in the context of the previous assessment.

Assessment for Potential Biases. The individual studies were examined for both reliability and validity noting their strengths and limitations. I examined the strengths and limitations of systematic reviews using the Assessment of Multiple Systematic Review (AMSTAR) tool.[26] I also noted whether the included epidemiologic studies considered the potential for biases in their overall assessment.[2,3] A recent meta-

analysis evaluated the epidemiologic studies using the New-Castle Ottawa Scale (NOS scale) and conducted sensitivity analysis to evaluate the influence of bias on results.[27] The New-Castle Ottawa Scale measures the potential for bias in non-randomized studies. It evaluates the potential for *selection bias*, the *comparability of control groups* and *outcome assessment* in cohort studies. In case control studies, it evaluates the potential for *selection bias*, *comparability* of cases and controls and biases due to *ascertainment of exposure*.

Weight of Evidence Approach. I have used a weight of evidence approach in examining the causal relationship between talcum powder products and ovarian cancer. I examined recent studies in the context of the cumulative body of scientific and medical evidence addressing the question of whether genital talcum powder use was causally related to an increase in the risk of ovarian cancer. I have relied upon my own update of the systematic review of the literature and the cumulative body of evidence as the basis of my opinions. This included gathering all relevant data based on *in vitro*, animal, and human epidemiologic studies on this topic since the initial assessment. Although the weight of my opinions is derived from findings published in the peer-reviewed literature, relevant unpublished documents are also noted when applicable. The individual studies were examined for both reliability and validity noting their strengths and limitations. The cumulative body of evidence was synthesized and examined and weighed using a widely accepted organizing framework - the Bradford Hill approach.[28] I also considered how understanding of data integration can inform causal inferences in the interpretation of these findings.[29] Using these materials, my education, and my prior clinical and research experiences, I employed the methods accepted by the scientific community that would be used to develop a peer-reviewed manuscript.

III. RESULTS OF SYSTEMATIC SEARCH

The results of the search yielded 122 citations, which after deduplication yielded 100 articles. The list of included and excluded studies is shown in **Appendix A**. The difference in the citation count of included and excluded articles reflects excluded duplicate articles retrieved from t[7]he two databases, the identification of articles noted in the previous report. Two exclusions are notable. I excluded a study on occupational exposure to talc[30] because of the lack of data on relevant routes of exposure and a study which evaluated the risk of survival among women with ovarian cancer with talc use because of the lack of data on risk of ovarian cancers among those exposed to genital talc use vs non-users.[31]

I included one umbrella review of systematic reviews,[2] and 3 systematic reviews and meta-analyses,[3,4,11,32] I also evaluated two pooled analysis of case control studies in the Ovarian Cancer Association Consortium (OCAC), [5,6] two pooled analyses of case-control studies Ovarian Cancer in Women of African American Ancestry (OCWAA) Consortium, [7,8]and one pooled analysis of cohort studies.[12] I also evaluated one case-control study.[9] I included 9 studies which reported on the biological plausibility of talc and the development of ovarian cancer.[13-17,20,33-35] I also examined the final report on screening assessment of talc by Health Canada,[10] and the results on testing for asbestos in talc by the FDA.[19]

IV. OVERVIEW OF SYSTEMATIC REVIEWS AND META ANALYSIS.

The three systematic reviews and meta-analyses,[3,11,32] including a data article by Taher et al.,[4] supporting a previous systematic review.[11] I also examined one umbrella review of systematic reviews.[2]

1. Woolen et al. conducted a systematic review and meta-analysis of case-control and cohort studies and examined the relationship between frequent perineal exposure to talcum powder, defined as multiple applications (≥ 2 times per week), and the risk of ovarian cancer.[3] Studies were included based on prespecified inclusion criteria including study size (n=10 cases), multivariable adjustment and defined research methods. They included 10 case control studies,[18,36-44] and data on the highest frequency talc exposure group from the Nurses' Health Study.[12] Only two studies in the O'Brien pooled cohort reported on the highest frequency of use, including NHS1 and Sister Study (SIS) study. The data from the SIS study were not shared and available for exclusion due to the small number of exposed individuals in the highest exposed category (n=2). The range of frequent talcum powder use was 4-7 times per week and 45% of studies (5/11) reported daily exposure.

The pooled odds ratio for frequent use of perineal talcum powder and ovarian cancer was statistically significantly increased at **OR 1.47 (95% CI 1.31-1.65)**, without any evidence of significant publication bias or significant statistical heterogeneity. The studies were homogenous and only 24.4% of variation across studies was due to heterogeneity. Even the odds ratio for the cohort study among frequent users was statistically significantly elevated at OR 1.40 (95% CI 1.17 to 1.68) and the pooled OR for case control studies was also statistically significantly elevated at 1.49 (95% CI 1.29- 1.72).

Woolen et al. also evaluated the quality of studies using the New Castle Ottawa Scale (NOS scale). The median NOS rating score of the included cohort study was nine and case control studies was 8, where 7-9 represents high quality study with low risk of bias. The results were robust to exclusion of the study by Booth et al., a study at elevated risk of bias (NOS score=4), or other studies at risk of bias, Cook et al. (NOS score=7),[38] and Whitemore et al. (NOS score=7),[43] without any change in estimates, estimates which remained statistically significant.

The overall higher magnitude of association seen in this analysis compared to previous meta-analyses, all of which have reported a statistically significantly increased risk,[1,45,46,11]is due to the emphasis on frequent use as opposed to any use, consistent definitions of exposure, and inclusion of higher quality studies in this study. Several study strengths are notable including the attempt to include unpublished data by contacting the O'Brien investigators. Their strengths and limitations are noted in the AMSTAR assessment in **Appendix B**.

2.Taher et al. evaluated 30 human studies. They retained 27 studies, including 3 cohort studies and 24 case control studies, for further quantitative analysis and noted a statistically significant positive association between perineal use of talc powder and ovarian cancer [**OR: 1.28 (95% CI: 1.20–1.37)].**[4,11] There was minimal evidence of statistical heterogeneity among included studies, suggesting a consistency of effects as the I^2=33%. Subgroup analysis by study quality [New Castle Ottawa Scale score < 7 vs > 7] did not show any differences in risk. Whereas a statistically significant risk was noted for case control studies (OR 1.32, 95% CI 1.24-1.40), meta-analysis of cohort studies showed an increased risk which was not statistically significant (OR 1.06, 95 % CI 0.9-1.25). There was no appreciable effect of the exclusion of a single study on the results. Results did not vary by decade of publication.

Their findings were consistent with multiple prior meta-analysis of earlier studies, all of which showed a statistically significantly increased risk comparing ever uses to never users.[1,45 46 11]

A significant risk was noted in Hispanics and Whites, in women applying talc to underwear, in pre-menopausal women, and in post-menopausal women receiving hormonal therapy (coherent with the

findings noted by Mandarino et al. which showed that estrogen accentuated the effect of talc).[17] They noted a negative association with tubal ligation.

Five studies reported evidence of a positive trend of an exposure response relationship, and two studies concluded that there might be a dose-response,[18,39-44] [Table 3 of the Taher publication],[11] whereas 11 studies were unable to detect an exposure response. They standardized exposure measurements into talc years and '*suggested a possible increasing trend in ovarian cancer risk with increasing exposure to talc"*. [Figure 3 of the Taher publication]. These findings on dose response are consistent with findings of Penninkilampi et al. who noted an increased risk of ovarian cancer with perineal talc use (OR = 1.31; 95% CI = 1.24, 1.39) and noted that more than 3600 lifetime applications (OR = 1.42; 95% CI = 1.25, 1.61) were slightly more associated with ovarian cancer than <3600 (OR = 1.32; 95% CI = 1.15, 1.50).[1]

3. Tanha et al. conducted an umbrella review of two systematic reviews and reported that perineal talc use was associated with a statistically significant increased risk of ovarian cancer **(OR 1.297, 95% CI 1.242-1.355: P<0.001)** without any evidence of statistical heterogeneity among included studies (I^2=0%).[2] Analysis using RR also showed similar results without any evidence of substantial statistical heterogeneity.

4. Lynch et al. conducted a systematic review and examined animal studies (n=4) and human studies (n=36) using the Institute of Medicine Framework.[32] They did not conduct a quantitative synthesis of the data. Their protocol stipulated the inclusion of meta-analysis and an assessment of their quality based on the AMSTAR scale, but these were also excluded based on a protocol amendment, the rationale for which was unclear. They did not include unpublished studies or solicit data from investigators. The strengths of the study include the inclusion of animal studies and evaluation of study quality using the IOM framework. However, the absence of any quantitative synthesis, their inability to assess other high quality epidemiologic studies including systematic reviews and meta-analysis and other limitations as noted in Appendix B limited the inferences that can be drawn from this study. As a result of these limitations, I placed less weight on this review as compared to other higher quality systematic reviews,[3,11] and assessment of the body of evidence in formulation my opinions.[10] However certain findings are notable.

They concluded that there was no association between perineal application of talcum powders and risk of ovarian cancer at human-relevant exposure levels. They acknowledged that the majority of case control studies (18/26=69%) reported a statistically significant increased risk of ovarian cancer with genital talcum powder use even after adjusting for multiple covariates. Health Canada identified that more than 92% of case-control studies have noted a positive association with the overwhelming majority of them being statistically significant.[10] These studies were conducted by various investigators in various settings during various time periods thus reducing the possibility of a confounding or bias as an explanation of an increased risk across all these studies. Among the five cohort studies included in their review,[47-51] they reported no statistically significant associations between genital talcum powder use and risk of epithelial ovarian cancer, but the majority of cohort studies also reported an elevated risk consistent with the case control studies. Three out of four cohort studies reported a positive association in the pooled analysis by O'Brien et al. However, cohort studies have significant limitations in their ability to detect an association between talc use and ovarian cancer which are detailed in **Section V.5.5**.

None of the cohort studies were designed to assess the risk of talc and ovarian cancer *a-priori*. The small number of cases included in the cohort studies significantly limits their statistical power to detect the

increased risk seen in the case-control studies. Narod et al. estimate that upward of 200,000 women would have to be enrolled in a cohort study to detect an effect of 1.2.[52] None of the individual cohorts enrolled such a large number of women. The number of ovarian cancer cases from case control studies is 6 times higher than the pooled cohort studies.[1] The Gates update of the NHS study was further limited by the low number of cases (n=29 cases among 108,870) which reduced their statistical power.[49] The study by Houghton et al. (Women's Health Initiative) also failed to detect a statistically significant effect because of limited statistical power (429 cases among 93,673 participants).[51] The cohort study by Gonzalez et al. (Sister Study) also reported on a small number of ovarian cancer cases.[50] As with the NHS and WHI, exposure was not updated during follow-up resulting in bias towards null. Cohort studies for talcum powder use did not consistently define the type of powder exposure, define changes over time, or capture duration and frequency of exposure.[3] The inability to update exposure during follow-up resulted in bias towards the null. In the Nurses' Health Study Gertig et al. assessed exposure as "never" use based only on a one-time question near the start of the study introducing unidirectional "behavioral change" bias, likely misclassifying some "ever" users who used talc during the study as "never" users; and biased the findings towards the null.[48] This was also seen in the WHI and the Sister Study by Gonzalez et al.[50] The short duration of follow up in some studies is a significant limitation (e. g., median 6.6 years in the Gonzalez et al. study) which may have biased their findings towards the null.[50] The study may have failed to account for latency period of ovarian cancer which is around 15-20 years. The Sister Study, similar to WHI and NHS, excluded women with a history of ovarian cancer at baseline, some of whom may have been talc users, and further biased their estimates towards the null. The inclusion of *prevalent users* rather than *new users* may have resulted in depletion of susceptibles biased their effects towards the null. [53]In some studies data on confounders were collected after baseline which resulted in adjustment of mediators for the talc and ovarian cancer relationship resulting in bias towards the null. Since exposure was not updated during follow-up, some never users who became ever users were misclassified as never users resulting in a bias towards the null.

Despite these study results which biased their findings towards the null, certain analysis of cohort studies also noted statistically significant increases in risk.

- Gertig et al. reported a statistically significant increased risk for ever talc use for invasive serous ovarian cancers in the NHS (**RR 1.40; 95% CI: 1.02–1.91**).[48]
- Woolen et al. noted that frequent use of talc was also associated with a significant increased risk of ovarian cancer in NHS1 **OR 1.40 (1.17-1.68**).[3]
- And most notably a significantly increased risk of ovarian cancer was seen in the pooled analysis of cohort studies by O'Brien et al. among women with patent reproductive tracts (**HR 1.13, 95% CI, 1.01 to 1.26**),[12] mechanisms of retrograde migration of talc and inflammation as a mechanism for development of ovarian cancer.[13,14]

V.**POOLED ANALYSIS.**

Pooled analysis of Case Control Studies in the OCAC Consortium

1. Phung et al. reported on a pooled analysis of 9 case-control studies in the OCAC to evaluate associations between well-established risk factors and risk of ovarian cancer among women with vs. without endometriosis (n=8500 women with ovarian cancer and 13592 controls).[5] One study was

conducted in Australia, one in Denmark and the other in USA. The analysis on talc use was limited to 8 studies conducted in US and Australia as no data on talc use was reported in the study from Denmark. All data were self-reported. These included first degree family history of ovarian cancer, tubal ligation, NSAID use, talc use, parity, BMI, hormonal oral contraceptive use, breastfeeding, duration of estrogen-only therapy, duration of estrogen-progestin therapy, age at menarche. Talc was characterized based on area of application (genital and non-genital) and non-users were the reference category. They addressed missing data on talc use in the studies using appropriate multiple imputation methods. Analyses adjusted for age, race/ethnicity, education, and any of the remaining 9 factors that changed the association between risk factor and ovarian cancer by ≥10 % in the final model. Genital talc use was statistically significantly associated with risk for ovarian cancer in women both with and without endometriosis with a higher risk among women with endometriosis than without endometriosis (**OR 1.38 95% CI 1.04-1.84 vs. OR 1.12 95% CI 1.01-1.25**: P for interaction =0.65]. These findings were consistent and coherent with the higher risk of ovarian cancer observed with talc use, because inflammation is one biological mechanism for the association between talc and ovarian cancer.[54]

2. Earlier in 2018 Peres et al. also pooled data from AACES study and 11 case-control studies in the OCAC to estimate the effect of 10 known or suspected ovarian cancer risk factors by race.[6] Among the 12 studies four did not report on body powder exposure and were excluded from analysis. Models were adjusted for age, study site and well-established risk factors with complete data across studies. Among 8 studies which evaluated genital powder use and invasive ovarian cancer, risk of invasive ovarian cancer was **statistically significantly higher among AA women (OR 1.62 95% CI 1.32-2) and non-Hispanic Whites (OR 1.30, 95% CI 1.20-1.41).** It was also increased among Hispanic but not statistically significant (OR 1.41; 95% CI 0.93 to 2.13). Genital body powder use was reported among 30% of White cases compared to 24% of controls, compared to 40% of AA cases and 31% of controls. Limitations include the fact that exposure data were obtained by self-report and missing data. However, combining AACES and OCAC minimized the impact of missing data.

<u>Pooled analyses of Case Control Studies in the OCWAA Consortium</u>

3. Davis et al. reported on a pooled analysis of five studies in the OCWAA Consortium (n= 620 AA cases, 1146 AA controls and n=2800 White cases and n=6735 controls) and evaluated the risk of ovarian cancer due to genital talc powder use,[8] by histotype and also evaluated the effect of frequency and duration. To improve the examination of heterogeneity they included studies with at least 40 AA cases and *exclusion of cases after 2013 to reduce the potential for recall bias*. The studies included the North Carolina Ovarian Cancer Study, Los Angeles Ovarian Cancer Study, Cook County Case Study, African American Cancer Epidemiology Study (AACES) and a nested case control study within the Women's Health Initiative (WHI). The AACES was included in the current analysis with restriction of case and controls to those interviewed prior to 2014. Controls within four studies were matched by age and race, with additional matching for ZIP code and geographic region for the Los Angeles County Ovarian Cancer Study and African American Cancer Epidemiology Study (AACES). Data on genital talc use was collected via self-administered or interview-administered standardized questionnaires. Genital powder was defined as any type of powder (baby, talc, deodorizing, cornstarch or unknown) applied directly to genital, perineal or rectal area or indirectly by sanitary pads, tampons or underwear. All studies assessed ever use and duration, while four studies assessed frequency. Frequency of use was categorized as no use, ≤ once per week, and > once per week. Duration of use was categorized as no use, < 20 years and ≥

20 years. Analyses were adjusted for age, education, duration of oral contraceptive use, family history of breast and ovarian cancer, tubal ligation, menopausal status, hysterectomy, interview year, BMI, smoking, and study site. The prevalence of genital powder use among cases was higher among AA women compared to Whites (35.8% vs 29.5%).

Ever use of genital powder was associated with a statistically significant risk of ovarian cancer among all women [OR 1.32, 95 % CI 1.17-1.48]. Ever use of genital powder was associated with statistically significant higher risk among white women (OR = 1.36; 95% CI = 1.19-1.57) although the 22% higher odds of ovarian cancer among AA women was not statistically significant [OR = 1.22, 95% CI = 0.97-1.53]. There was no evidence of heterogeneity by race (P=0.33). In AA women, the positive association with risk was more pronounced among high-grade serous tumors (OR = 1.31, 95% CI = 1.01-1.71) than with all other histotypes (OR = 1.05; 95% CI = 0.75-1.47). The authors concluded that while genital powder use was more prevalent among AA women compared to Whites, **the significantly increased risk of ovarian cancer with talc use was similar across race and did not vary by histotype**. This study is notable for several reasons.

It estimated the **Population Attributable Risk (PAR)** of ovarian cancer as a result of genital talc exposure. The PAR represents the proportion of the incidence of a disease in the population (exposed and nonexposed) that is due to exposure.[55] **In other words the incidence of disease in the population that would be eliminated if exposure was eliminated**. They estimated that the overall **PAR was 6.4% (95% CI= 2.2 to 10)** and similar between AA women (7.5% 95% CI =6.5 to 8.5) and White women (6.2 %; 95% CI =5.4 to 6.9) **Thus 6.4% of all ovarian cancer in the population would be eliminated if there was no genital talc exposure.**

Although recall bias remains a concern for all case control studies, the exclusion of interviews conducted after 2014 diminished the potential for recall bias due to any potential stimulated reporting occurring after the onset of talcum powder lawsuits in 2014. It addressed any potential for recall bias in the AACES study by excluding case and controls interviewed after 2014. The AACES study reported a statistically significant increased risk of ovarian cancer among AA women overall (1.44, 95% CI: 1.11 to 1.86),[42] with the estimates being attenuated when analysis was restricted among women evaluated prior to 2014 (OR 1.19, 95% CI 0.87 to 1.63) compared to those interviewed after 2014 (OR 2.91 95% CI 1.70 to 4.97). **Notable AACES reported significant trends for frequency and duration of use.**

There was no difference in the association by frequency of genital powder use, although both reported a significantly increased risk (≤ once per week OR= 1.34, 95% CI 1.01 to 1.79) and more than once per week (OR 1.31, 95% CI 1.15 to 1.48, P_{trend}=0.98). Similar trends were observed when examined by race. No dose-response trends were observed overall with duration of use and when stratified by race.

4. In 2021 Peres et al. also used data from case-control studies and cases-control studies nested within prospective cohorts in the OCWAA Consortium to estimate race-specific associations of 10 known or suspected EOC risk factors including body mass index, Oral contraceptive use, full term pregnancy, tubal ligation, first degree family history of breast cancer, first degree family history of ovarian cancer, aspirin use, genital use of body powder, education and endometriosis. [7] The OCWAA includes data from four case-control studies: the African American Cancer Epidemiology Study (AACES), the Cook County Case-Control Study (CCCCS), the Los Angeles County Ovarian Cancer Study, and the North Carolina Ovarian Cancer Study ; and 4 case-control studies nested within prospective cohorts: the Black Women's Health Study the Multiethnic Cohort Study, the Southern

Community Cohort Study, and the Women's Health Initiative (WHI) including both clinical trial and the observational study. The Southern Community Cohort was not used for their analysis limited to 4 case-control studies and 3 nested case-control studies in cohorts. The analysis for baby powder further excluded data from the Black Women's Health Study, Multiethnic Cohort Study, and WHI non-observational group because body powder exposure was not asked in the questionnaire. Due to potential reporting bias of the lawsuits, data were restricted to women diagnosed before 2014.

After adjusting for known risk factors study site, reference year, age at diagnosis, age at menarche, menopausal status and history of hysterectomy 1 year before diagnosis ever use of baby powder applied to genital area was associated with a statistically significantly increased risk of ovarian cancer among both AA women **(OR 1.36, 95% CI 1.10 to 1.70)** and whites **(OR 1.28, 95% CI 1.15 to 1.43).** The PAR for baby powder use in the genital area was 10.3 %(95 % CI 3.1% to 17.1%) among AA women and 6.5%(95% CI 3.3% to 9.3%) among white women. Strengths include the use of multi-level multiple imputation methods to account for missing data. The increase in risk for ovarian cancer with ever use of body powder applied to genital area did not appreciably change and remained statistically significant for AA women (OR 1.35, 95% CI 1.04 to 1.74) and whites (OR 1.27, 95% CI 1.13 to 1.41) after multiple imputation. It also excluded interviews conducted after 2014 to diminish the potential for recall bias due to any potential stimulated reporting. Limitations include the fact they excluded certain risk factors, including menopausal hormonal therapy, breast feeding and smoking from analysis. They stated that these exposures are associated with ovarian cancer in subpopulations (hormone therapy among postmenopausal women, breast feeding among pregnant women) or are associated with specific subtypes (smoking and risk of mucinous tumors).

Pooled analysis of cohort studies

5. O'Brien et al. pooled data from four US based cohort studies including the Nurses' Health Study, Nurses' Health Study II, Sister Study and Women's Health Initiative Observational Study.[12] They examined the association between ever, long term (≥ 20 years) and frequent (≥1/week) use of powder in the genital area and self-reported incident ovarian cancer using Cox-proportional hazards model. The pooled sample included 252,757 women with a median age at baseline of 57 years with 38% self-reporting use of powder in the genital area. Ten percent reported long term use and 22% reported frequent use. They selected confounders based on directed acyclic graphs at baseline and excluded women with ovarian cancer or oophorectomy prior to baseline.

Despite the median 11.2 million years of follow-up, the number of ovarian cases was small (n=2168). The incidence was 61 cases/100,000 person years among ever users compared to 55 cases/100,000 person years among never users. The overall estimated risk [HR 1.09, 95% CI 0.99 to 1.17] did not show a significantly increased risk.[12] However the authors acknowledged "***that the lack of statistical significance did not equate to evidence of no association*".** [56]

However, they conducted a *prespecified* analysis evaluating the risk of ovarian cancer among women with patent reproductive tracts (defined as having a uterus and no tubal ligation) based on the consideration that such women were more susceptible to the effects of talc. This analysis showed a statistically significant excess risk for ever users and never users even after adjustment for various risk factors. O'Brien "***agreed that the positive association among users with patent reproductive tracts (HR 1.13, 95% CI 1.01- 1.26) is consistent with the hypothesis that there is an association between genital powder use***

and ovarian cancer".[56] [57] Other epidemiologic studies have also noted a significantly increased risk of ovarian cancer among with no tubal ligation compared to those with tubal ligation. [40]

Study limitations are highlighted below and were noted by Cramer et al.[58] and Harlow et al.[59]

Exposure measurement. There are differences in assessment of duration and frequency of exposure and assessment of use as a time-varying factor. As an example, in the Sister Study, exposure frequency was 14% when exposure in the past year was considered and 27% when exposure at age 10-13 years was considered.[58] The cohort studies were unable to examine specific exposure windows. O'Brien et al. acknowledged that information on powder exposure is typically more limited in cohort studies than case control studies, particularly with dose and duration of use. None of the studies had information on whether talc or cornstarch was used, and none had information on both frequency and duration of use to truly assess dose-response.[58] The widely varying definition of ever exposure among the four cohorts resulted in more misclassification and bias towards the null. The authors acknowledged that this lack of detail may have biased their findings towards the null.

Unidirectional behavior change bias. The inability to update exposure during follow up assumes that cohort members who had been exposed at baseline, such as 34 years prior in the NHS, remained exposed during the entire study period.[58] It is likely that some in the unexposed group were exposed to powder in the follow up period, attenuating any risk differences between exposed and unexposed groups.

Age and Menopausal status at Exposure Assessment. Cramer et al. noted,[58] that most of the women enrolled in the study were post-menopausal at time of assessment of exposure, whereas risk of talc induced ovarian cancer is highest among pre-menopausal women and or post-menopausal women who use estrogen.[50]

Depletion of susceptibles. Since the median age of assessment of exposure was 57 years, several decades after first exposure and they restricted outcome assessment to women who survived to this period, this resulted in *depletion of susceptibles* and resulted in bias towards null.[59]

Measurement of confounders after baseline. The assessment of confounders long after exposure assessment can lead to control for mediators that can attenuate causal effects and bias findings towards the null. [59]

Inability to assess tests for patency. The authors acknowledged that they did not perform tests for patency, so women reported as being patent in this analysis may not have patent reproductive tracts biasing the findings towards the null. Despite these limitations which bias their findings towards the null the 13% significantly increased risk of ovarian cancer with genital powder use seen among women with patent reproductive tracts was greater than the 10% increase in cancer attributable to 10,000 or more applications in women with intact genital tracts. [59]

Limited statistical power. The number of cases of ovarian cancer in 24 case control studies (n= 13421)[1] is more than sixfold higher than the number of cases of ovarian cancer reported by O'Brien et al (n=2168) demonstrating the limited power of cohort studies to detect a significant increase in the risk of ovarian cancer

Interpretation of P-values. The authors interpreted an HR of 1.08 with a lower bound of 0.99 as being no evidence of an association which is inconsistent with the American Statistical Association statement on the appropriate interpretation of P-values.[60]

Residual confounding is always possible in an observational study.

Generalizability. The generalizability of study findings among white well-educated women, half of whom had a BMI of less than 25 and median age of 57 years to a younger, obese and or more ethnically diverse cohort is limited.

Despite several limitations, which attenuated their findings towards the null, the 13% significantly increased risk of ovarian cancer seen in the pooled analysis of cohort studies by O'Brien et al. among women with patent reproductive tracts (HR 1.13, 95% CI, 1.01 to 1.26) is in line with the cumulative body of epidemiological evidence,[1] and with the biologically plausible mechanism of talc induced retrograde migration and inflammation as a mechanism for development of ovarian cancer.[13,14] Data from 24 case-control studies and three cohort studies conducted over several decades by several investigators have consistently shown an increased risk without substantial heterogeneity (OR 1.31,95% CI1.24 to 1.39),[1] confirmed in recent analysis of case control and cohort studies.[3,11]

The strengths of the cohort studies are also to be noted. They are less prone to recall bias and recall bias remains a concern among the case control studies.

Recall bias in case-control studies. Some amount of recall bias is possible in the case-control studies.

- Although biases, particularly recall bias, are a concern in case-control studies they may not be a significant concern when exposure is simple (never vs ever). Many of the case control studies addressed the issue of recall bias by including questions of talc use as a part of extensive questionnaires. [1]
- The role of media attention is important but most case control studies except by Schildkraut et al.[42] were conducted prior to 2014 and analysis of AACES by Davis et al. and Peres et al. excluded cases after 2014 correcting for this potential bias.[7,8]
- The fact that the association was stronger for certain histologic types and there was no evidence of corn starch use in a case control study,[18] argues against the presence of significant recall bias.[58]
- Cramer et al. included a 18% buffer to account for recall bias before nullifying their study results.[18]
- To conclude that there is no evidence of an increased risk between genital talc use and ovarian cancer would require the presence of a substantial and pervasive degree of differential recall bias operational across the cumulative body of evidence from twenty-four case-control studies to negate the findings of a consistently positive association between talc use and ovarian cancer. The presence of such a significant and pervasive degree of differential recall bias between cases and controls among studies conducted by different investigators, across different time periods is highly implausible.

VI.CASE-CONTROL STUDY.

Gabriel et al. used data from a previous case control study,[18] to examine the joint effects of douching and talc use on risk of epithelial ovarian cancer (n=2040 cases; n= 2100 controls).[9] Models were adjusted for study matching factors (age, study center phase), parity, OC use, BMI, race, diaphragm use, spermicide use, menopausal status, marital status, smoking, days of menstrual flow, age of menarche and tubal sterilization. **Women who used talc had an elevated risk for ovarian cancer overall compared to those who did not, OR 1.30 (95% CI 1.13, 1.50).** The ORs for talc use in relation to epithelial ovarian cancer were similar among women who had also regularly douched, OR 1.32 (95% CI 0.95, 1.82) and those who had not, OR 1.28 (95% CI 1.09, 1.51). Excluding women with tubal ligation slightly lowered these

estimates but did not change their significance; OR: 1.23 (95% CI 1.05, 1.44) for talc use overall, OR: 1.33 (95% CI: 0.92, 1.92) for talc and douching, and OR: 1.19 (95% CI 1.00, 1.42) for talc alone. Risks were greater for women who began talc use during their 20's regardless of douching. **There was evidence of dose-response trend with increasing talc years (P_{trend}=0.0006).** Although there was an excess risk for ovarian cancer among each duration category of exposure (> 1-5 years; >5-24 years and > 26 talc-years), the risk was statistically significant for > 26 years at OR 1.51 (95% CI 1.12 to 2.03).

VII.BIOLOGICAL PLAUSIBILITY.

I evaluated several studies which reported on biologically plausible mechanisms of genital talcum powder use and an increase in the risk of ovarian cancer.[13-17,20,33,34,35]These studies provide evidence on retrograde migration of talc particles,[14,16] [13] promotion of inflammation,[13,17] and demonstrated that talc particles, especially in the context of increased estrogen, impair the tumoricidal function of macrophages [17] as detailed in the **Section VIII : Mode of Action in the Health Canada report** below.[10] Some new studies published after the evaluation by Health Canada on biological mechanisms are noted below.

Harper et al. evaluated the exposure of normal primary ovarian epithelial cells (HPOE), ovarian epithelial cells (HOSEpiC) and primary fibroblasts to talcum powder (100 or 500 μg/) or controls (titanium dioxide) for 72 hours and assessed their effects via a cell transformation assay and immunochemistry.[33] Treatment with talc resulted in the formation of colonies indicating malignant transformation in a dose-dependent manner in ovarian cell lines.[33] Transformed ovarian cells were increased by 11% and 20% in HPOE and 24% and 40% in HOSEpic cells for talcum powder 100 and 500 μg/mL doses, respectively (P<0.05). This transformation was not seen when cells were exposed to controls (Titanium dioxide) or untreated ovarian cancer cells. Exposure of primary fibroblasts to talc also did not result in malignant transformation. They provided evidence that exposure to talcum powder induces malignant transformation in ovarian epithelial cells but not in primary fibroblasts which represents a direct effect of talcum powder specific to normal ovarian cells and provides further support of previous studies demonstrating the increase in the risk of ovarian cancer with genital talc talcum powder use.

Building on the findings of Mandarino et al. described in Section VIII Mode of Action below,[17] where talc impaired the tumoricidal activity of macrophages, Emi et al. performed gene chip microarray profiling and found that talc alone, and especially with estrogen, has substantially more prominent gene expression than titanium dioxide.[17] These affected genes were involved in cell proliferation, immune response and regulation, and enzymes and proteins of epigenetic regulation. This explains the findings of reduced tumoricidal activity of macrophages noted by Mandarino et al.

Role of Asbestos. Because talc is mined in close proximity to asbestos, it is also important to consider the role of asbestos in evaluating an increased risk of ovarian cancer with talcum powder use. The FDA, Johnson & Johnson's testing, and the analyses of Drs. Longo and Rigler have documented the presence of asbestos in talcum powder products, an established cause of ovarian cancer.[19,20,21,22,23] Asbestos is classified as a Class 1 carcinogen along with asbestiform talc. [24,25] Asbestos is an indisputable risk factor for ovarian cancer as noted in the IARC report and meta-analysis of epidemiologic studies.[23,24,25] The editor of the *American Journal of Public Health* Dr. Morabia noted that '*asbestos is an established carcinogen*" and '*Commercial talcum powder, such as baby powder, is a mineral product extracted from rock ore dug from mines, originally in Italy and later in Vermont. It is a mix of hydrated magnesium silicate with other minerals, including asbestos fibers*."[61]

This detection of asbestos should be seen in the context of Food and Drug Administration's efforts to guarantee that talc was up to 99.99% free of chrysotile and 99.9% free of amphibole asbestos.[62] A recent article noted, "*cosmetic talc powder manufacturers, through their trade association, pressed for a less stringent methodology and adopted the term "nondetected" rather than "asbestos-free" as a term of art.*" [62] Despite the emphasis on this less stringent methodology, studies have continued to show the presence of asbestos in talc.

In 2019, FDA commissioned testing which identified the presence of chrysotile asbestos and talc fiber in samples of Johnson's Baby Powder Lot #22318RB and Johnson & Johnson recalled this lot.[19]

A study on 10 cases of ovarian cancer among those with genital talc exposure and evaluated talc in tissues and asbestos exposure.[20] They detected talc in all cases and asbestos (tremolite and/or anthophylite asbestos) in 8/10 cases. The asbestos fibers found in the "cosmetic" talc containers matched those found in tissues. The estimated inhaled asbestos dose ranged from 0.38 to 5.18 fiber years. They concluded that inhaled dose of *asbestos/fibrous talc* from "cosmetic" talc use causes ovarian cancer. They also modelled a dose-response analysis and reported that the risk of developing ovarian cancer due to inhaled asbestos exposure was calculated to be 2.3 to 31.1 times greater in these cases compared with baseline risk for ovarian cancer, with an average 7.7 higher risk among cases.

In 2021 Vimercati et al. reported on a case series of 4 cases with primary ovarian mesothelioma, of whom two had exposure to cosmetic talc.[35] Among the two cases with talc exposure, scanning electron micrography identified amphibole fiber tremolite in one case.

VIII. HEALTH CANADA REPORT.

Health Canada examined the cumulative body of evidence concluding that database was robust to arrive at confident conclusion of a causal relationship between perineal talc exposure and ovarian cancer.[10] Notably, the assessment included the pooled cohort by O'Brien et al. and they reached their conclusion assuming that cosmetic-grade talc used in the assessment was free of asbestos, an established cause of ovarian cancer.[24] Their assessment also preceded the publication of several systematic reviews,[3] pooled analysis of case control studies ,[5,8] and studies on biological plausibility,[33,34] which have provided further evidence in support of a causal association. Their key findings with the emphasis on the new studies are noted below.

Mode of action

Retrograde migration of talc. The report noted that talc could migrate to the ovaries from perineal use,[63,64] and also noted the potential for talc particles in the ovaries.[65] In 2014 the US FDA noted that "*the potential for particles to migrate from the perineum and vagina to the peritoneal cavity is indisputable. It is therefore plausible that perineal talc (and other particulate) that reaches the endometrial cavity, Fallopian tubes, peritoneum and ovarian may elicit a foreign body type reaction, and inflammatory response, that in some women may progress to epithelial ovarian cancer*."[66]

McDonald et al. conducted a study to differentiate talc exposure vs contamination in pelvic lymph nodes from ovarian cancer patients some with documented talc exposure.[14] Pelvic lymph nodes in 22 patients with ovarian tumors were examined by digestion and regular scanning electron microscopy/energy dispersive Xray analysis (in-situ SEM/EDX). Genital talc users had higher talc counts than non-users of

borderline significance. After adjusting for surface contamination, talc burden in nodes correlated strongly with genital talc use.

McDonald et al. conducted another study among 5 patients with perineal talc use and 6 negative exposure controls and showed that talc particles were found in pelvic sites including pelvic lymph nodes, cervix, uterine corpus, fallopian tubes and ovaries using in-situ scanning electron micrography (SEM) and transmission electron micrography -- ideal for measurement as they preserve architecture and allow determination of contamination.[13] Among the 6 controls, two patients with a history of pelvic and surgical procedure had four particles which may have been introduced from environment or from gloves. They also showed that macrophages ingested talc consistent with the inflammatory mechanism of talc in increasing the risk of ovarian cancer.

Johnson et al. provided additional proof of retrograde migration of talc particles by comparing talc particles in commercially available powders to those found in pelvic tissues from randomly selected ovarian cancer patients with known history of long-term perineal talc exposure.[16] Polarized light microscopy and SEM/EDX was employed to measure talc particles after extensive measures to control for contamination. The particle size and dimensions of talc particles found in commercial samples were consistent with those found in the pelvic tissues: 77.7% of commercial samples and 83.5% of pelvic samples fell within the same ranges of aspect ratio and area supporting the assertion that externally applied talc can migrate from the perineal area.

Inflammation. The report identified several studies that support the conclusion that talc exposure may lead to ovarian cancer through inflammatory mechanisms.[15] Local chronic irritation can lead to an inflammatory response, one mechanism of talc induced ovarian cancer.[67] Inflammation is a risk factor for ovarian cancer,[68] and elevated levels of CRP[69] are associated with a significantly increased risk of ovarian cancer.

Fletcher et al. showed that talc treated cells demonstrated a dose-dependent increase in prooxidant inducible nitric oxide synthetase, nitrate/nitrite and myeloperoxidase and a decrease in antioxidants catalase, superoxide dismutase, glutathione reductase and glutathione peroxidase ($P<0.05$).[15] Talc showed an increase in inflammation as shown by a significant increase in CA-125 ($P<0.05$). Talc also induced proliferation and decreased apoptosis in cancer cells and normal cells ($P<0.05$).

Mandarino et al. using phagocytic murine cell lines and murine ovarian surface epithelial cell line as prototypic ovarian cell lines examined the effect of macrophages treated invitro with talc, especially in a high estrogen environment.[17] Talc alone, and especially in combination with estradiol, introduced changes in gene expression that promoted a pro tumorigenic environment and less efficient tumoricidal activity of macrophages. Exposure to control particles such as titanium dioxide, urban air particles and diesel exhaust did not demonstrate these deleterious effects. Although the authors did not investigate whether the inhibited tumoricidal activity could entail an increased likelihood of tumor growth they concluded that "*our findings can help reconcile the presumed innocuous nature of talc with epidemiological data on talc powder use and OC risk by suggesting that the effect can be mediated by the macrophages*." These findings are consistent with the highest risk of ovarian cancer among pre-menopausal women, and post-menopausal women exposed to estrogens. Sato et al. noted that talc induced a greater inflammatory response than other particles in a recent study in hamsters,[70] and the Health Canada report concluded that talc "*demonstrates tumour-promoting activity*".

Immune mediated. Another mode of action was noted via immune related mechanisms. In this case talc, need not reach ovary but only needs to reach the lower genital tract where they could trigger immune mediated changes such as the production of heat shock proteins and decreased level of antibodies.

Human studies

Several published epidemiological studies have consistently reported a positive association between perineal talc exposure and ovarian cancer with ORs ranging from 1.22 to 1.35 [1,11,46]. Collectively, approximately 30 case control studies and four cohort studies produced similar OR's despite selecting different studies and adjusting for different set of confounders. A high percentage of the case control studies -- 89% in Berge et al,[46] 92% in Penninkilampi et al,[1] and 85% for Taher et al,[11] had ORs >1 indicating a positive association. Approximately half of these were statistically significant. Although 3 of the 4 cohort studies reported an increased risk, none of them were statistically significant except for a statistically significant increased risk among women with patent reproductive tracts overall, [12] as well as the invasive serous ovarian cancer sub-type.[1]

Cohort studies.

Gertig et al. and Gates et al. reported on the same Nurses' Health Study cohort.[48,49] Only 71% of participants returned the mailed questionnaires. The questions pertaining to perineal powder use were asked only once in 1982. They were asked if they ever commonly used talcum, baby or deodorizing powder applied to perineal area or sanitary napkins. Although Gates et al. followed participants for 24 years, they combined never users with those that used powders less than once a week biasing their findings towards the null. Gertig et al. accounted for never users, but their study had only a 14-year follow-up period. Both studies lack detailed exposure data, resulting in exposure misclassification because of the lack of specificity around talc exposures.

Gonzalez et al. reported data from the Sister Study in 2016 among women who had a sister diagnosed with breast cancer.[50] Although questions were specific to talc powder use, the questions focused on use during the ages of 10-13 years and past 12 months. It reported 154 incidents of ovarian cancer cases among 41,654 participants. **It had the shortest duration of follow up (median of 6. 6 years)** which failed to account for the latency period of ovarian cancer, and as a result, it produced the lowest HR (HR 0.73, 95% CI 0.44 to 1.2) among the cohort studies. It reported a significantly increased risk of ovarian cancer with douching among the cohort studies. The authors recognized the limitations of the short duration of follow up and the limited duration of assessment of talc exposure.

Houghton et al. reported on the Women' Health Initiative (WHI) cohort on post-menopausal women between the ages of 50-79 years with a mean follow up of 12.4 years.[51] They included 61, 576 participants with 429 adjudicates cases of incident ovarian cancer. Similar to the NHS, the questions were not specific to talc but queried general perineal powder use, similar to the NHS and only measured via self-report at baseline. They did not have any information on talc powder use. They accounted for duration but not frequency of use. The authors noted the lack of information on oophorectomy after exposure which would result in inclusion of women not at risk of ovarian cancer and bias their findings towards the null. Non-differential misclassification of exposure biased their findings towards null.

The NHSII was the new study in the O'Brien et al. analysis. The NHS II cohort focused on oral contraceptive use and was a younger cohort (age 25-42 years). The response rate for mailed questionnaires was less than 25%. Only four years of follow up data was available for the analysis

because the questions on perineal powder use (at least weekly) were not added until 2013 which means that only 4 years of follow-up was available for the O'Brien et al. analysis. The median age of ovarian cancer diagnosis is 63 and two of the cohorts (NHS II and SIS) comprising 40% of sample size are made up of younger group of participants, an age group where the cancer incidence may not be detectable.

The Health Canada report noted that the study by O'Brien et al., as acknowledged by the study authors, may have been underpowered to detect an increase in the risk. Significant limitations of the O'Brien et al. analysis are noted in **Section V.4.5.**

Case-control studies

The number of ovarian cancer cases in the 30 case control studies is substantially larger than the largest pooled cohort analysis with data from different countries and ethnic groups. The variation in prevalence of talc use varied among cases and controls and could reflect ethnic differences in talc exposure.[71] There was substantial variation in response rates among the studies. The majority of studies used population-based controls. Importantly assessment of talc use was either administered via in-person or telephone interviews by trained staff versus self-administered. Some studies focused on talc use in the context of various risk factors diminishing the potential for recall bias. Study limitations of the individual case control studies included small sample sizes, limited exposure information in the earlier studies, self-reported data, low response rates and the potential for recall bias.

Evidence of causation by Health Canada.

They evaluated the evidence of causation using the Bradford Hills viewpoints with a focus on strength, consistency, biological gradient and biological plausibility. Temporality is a prerequisite for establishing that a given risk factor is causal. They highlighted that experiments, analogy and specificity are often considered less significant in decision making.

Strength. Although large precise RRs increase confidence in the causal relationship that RRs may not be due to chance, bias or confounding, risks of modest magnitude do not preclude a causal relationship as they may represent low level of exposure or a rare disease.[72] They noted that a high proportion of available case control studies representing a broad section of the population have reported strikingly similarly OR. Since ovarian cancer is a rare disease, the considerable number of studies giving similar results is important to note. They noted that RR's range from 1.22 to 1.35 which are modest, but precise, statistically significant with narrow confidence intervals. Since the publication of the report, studies that focused on frequent users reported even higher risks (RR 1.47),[3] providing further support of the strength of an association between perineal talc use and an increased risk of ovarian cancer.

Consistency. The studies reported were conducted over different time periods, by different investigators using various methodologies. They included different ethnicities and spanned many countries. Despite these differences they provide consistent evidence of an increased risk with ORs from newer studies being similar to ORs from older studies. There was no evidence of substantial heterogeneity among the included studies.[1,11] The I^2 was 10.52% in the study by Penninkilampi et al. which indicates the presence of homogeneity (I^2 = 25% is low heterogeneity and I^2=50% is moderate statistical heterogeneity).[1] The absence of statistically significant excess risk in some of the cohorts should not be taken as evidence of inconsistency. Overall, 91% of epidemiologic studies examined reported a positive association between talc use and ovarian cancer. Besides a CI that contains null also contains non-null values of importance and should not be dismissed.[73] These overlapping confidence intervals in the case control and cohort

studies are not evidence of inconsistency but indicate differences in design, study methods, and populations. Cohort studies minimized recall bias and selection bias but require longer follow up times and larger number of cases for rare outcomes to achieve statistical power. It is unknown whether follow up period of the cohorts was adequate to detect a potential association between perineal talc exposure and ovarian cancer. The cohorts, even when pooled together, may not be sufficiently powered as the number of ovarian cancer cases in case control studies as noted by Penninkilampi et al (n=13,421)[54] is six times larger than the largest pooled analysis by O'Brien et al. (n=2168 among 252, 745 participants).[12]

Biological gradient. Meta-analysis conducted by Penninkilampi et al. provide some evidence of a dose-response in the form of an increasing risk seen with increasing number of applications.[1] The new studies by Taher et al identified seven studies that reported increased risk of ovarian cancer with increasing perineal application of talc.[11] However it is important to note that a linear dose-response may not characterize the induction of ovarian cancer by talc because it is difficult to adequately model dose-response relationships.

Plausibility. Overall the report concluded that available animal and human data clearly indicate that talc particles were capable of retrograde migration into the pelvis and ovarian tissue causing inflammation and several recent studies provide supportive evidence perineal talc exposure leading to ovarian cancer is biologically plausible.[13-15,17] Recent research with respect to specific mechanisms (inflammation and precursor events) provide support to their conclusions on a plausible biological mechanism on how talc may increase the risk of ovarian cancer.[33,34]

Role of chance, bias and confounding.

Chance: They emphasized that chance is unlikely to play a significant role given the ORs are statistically significant results across the majority of studies.

Confounding: Age, race, low parity, infertility, and a family history of ovarian cancer are among the risk factors with age and parity considered key. Most of these human epidemiologic studies adjusted for a variety of these potential confounders. Although it is possible all the potential known and unknown confounders may not have been eliminated, significant efforts have been made to adjust for the recognized confounders. Again, it would require the presence of a significant confounder pervasive across these studies conducted in various locations by different investigators to dilute findings towards the null. Such a confounder appears implausible.

Bias: Although biases, particularly recall bias, are a concern in case-control studies they may not be a significant concern when exposure is simple (never vs ever). Many of the case control studies addressed the issue of recall bias by including questions of talc use as a part of extensive questionnaires.[1] Cramer et al. included a 18% buffer to account for recall bias before nullifying their study results.[18] The role of media attention is important but most case control studies except Schildkraut et al.[42] were conducted prior to 2014 and analysis of AACES by Davis et al. and Peres et al excluded cases after 2014 correcting for this potential bias. [7,8] The limitations of the cohort studies are noted in **V.4.5**

Ovarian cancer-weight of evidence.

The report concluded that database was robust to arrive at confident conclusions of a causal relationship between talc exposure and ovarian cancer. They concluded :

'While animal models are generally inadequate to assess ovarian cancer risk, the available animal studies (noting inflammatory response to talc and the ability of talc particles to migrate up the reproductive tract) support biological plausibility and results were consistent with a possible human mode of action for cancer development. The database is large, and while cohort and case-control studies generally gave different results, the overall database provides adequate information to assess the risk of ovarian cancer due to talc exposure. There is the potential for perineal exposure to talc from the use of various self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs, bubble bath). Characterization of ovarian cancer risk is qualitative in nature as a clear dose response for ovarian cancer could not be derived from the available literature. Data from meta-analyses of epidemiological studies indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2019). Although some authors note concerns with regard to bias in the literature, considering the available lines of evidence, the current data are indicative of a causal effect.'

Recent epidemiologic studies,[2,3,5,7] evidence on biological plausibility,[33,34] and analyses demonstrating the presence of asbestos in talcum powder products,[19,20,21,22,23] provide additional evidence in support of a causal association between perineal talcum powder use and ovarian cancer.

IX. BRADFORD HILL VIEWPOINTS.

The cumulative body of evidence was appraised using the Bradford Hill viewpoints. I put significant weight on the *Strength, Consistency, Temporality, Plausibility, and Coherence* viewpoints and, to a lesser extent, Gradient (Dose-Response) and Analogy data to support my opinion that Talcum Powder Products can cause ovarian cancer. For the reasons stated below, I do not heavily weigh the Experiment and Specificity data in light of the totality of the evidence supporting a causal inference. My assessment is described below.

Strength of Association. Hill's first criterion for causation is *strength of the association*. Defining what constitutes a "strong" association is critical to the assessment of potentially causal relationships.[29]
The findings from several new systematic reviews and meta-analysis,[3,4] umbrella reviews of systematic reviews,[2] pooled analyses of case-control studies,[5-8] and new case control studies,[9] provide further evidence that talc is associated with an approximate 30-60% **precise and statistically significant increase** in the risk of ovarian cancer, after adjustment for multiple confounders of the talc and ovarian cancer relationship.[1,11,46] Even among the cohort studies which are limited in their ability to detect an exposure outcome association, the majority continue to report ORs > 1. There continues to be a significantly increased risk among women with patent reproductive tracts in the cohort studies.[12] The Health Canada report noted that these RR's were range from 1.22 to 1.35 which are modest, but *precise, statistically significant with narrow confidence intervals.* The newer analyses which have focused on frequent uses have noted a higher magnitude of risk compared to studies comparing ever users with never users. [3] These risks of modest magnitude do not preclude a causal relationship as they may represent low level of exposure or a rare disease.[72] There are several noteworthy examples of well-established causal relationships where the strength of the association is in the order of 20-40%.Second hand smoking is an established carcinogen with an excess risk is of the order of 20% for women and 30% for men.[74] Such causal associations can have significant effects on the population. Davis et al. estimated that 6.4% of the ovarian cancer in population would be eliminated if talc was removed from

the environment. [8]

Consistency. Evidence of consistency is provided by evidence from new systematic reviews and meta-analysis,[3,11] case controlled studies,[9] and several pooled analysis of case-control studies.[5-8] As shown in detail above, the direction and strength of association of talc and ovarian cancer is generally consistent across studies, including observational studies of various designs and their meta-analysis, and observational studies. These studies have been conducted in different clinical settings across the world, with different duration of follow up and the cumulative evidence has consistently shown a significantly increased risk of ovarian cancer with the use of talcum powder products. They included different ethnicities and spanned many countries. Despite these differences they provide consistent evidence of an increased risk with ORs from newer studies being similar to ORs from older studies. As expected, there are slight differences in the point estimates which reflect differences in study population with all point estimates showing a direction of increased risk of ovarian cancer. The confidence intervals, however, across study designs overlap, indicating consistent results. I place significant weight on the fact that the consistency and strength of the association found in multiple independent studies demonstrates that the association is causative.

The findings of the cohort studies are not inconsistent and can only be interpreted in the context of cumulative body of evidence of an increased risk from several case-control studies.[12] A high percentage (91%) of the epidemiologic studies examined had ORs > 1 and overall consistent values despite being conducted by different investigators using varied methodologies as noted in the Health Canada report.[1] Despite the limitations such as latency, limited statistical power, exposure misclassification, depletion of susceptibles which biased the findings towards the null, the findings of a non-statistically significant increased risk in the cohort studies overall, and a statistically significant risk among women with patent reproductive tracts, should not be deemed inconsistent. O'Brien et al. showed a significantly increased risk among women with patent reproductive tracts (HR 1.13, 95 % CI 1.01 to 1.26) and an elevated risk overall that failed to reach statistical signficance.[12] A pooled analysis of cohort studies also showed evidence of invasive serous type ovarian cancer (OR 1.25, 95% CI 1.01 to 1.55).[1]

There was no evidence of substantial statistical heterogeneity among the included studies as noted in the estimates of the I^2 in recent umbrella review of systematic reviews (I^2%=0%) and several meta-analysis.[1,3,11] I^2 = 25% represents low statistical heterogeneity and I^2=50% represents moderate statistical heterogeneity. The meta-analyses by Woolen et al. (I^2=24.4%) and Taher et al. (I^2= 33%) reported no evidence of substantial heterogeneity similar to the earlier meta-analysis by Penninkilampi et al (I^2=10.52%).[1] This presence of homogeneity is evidence of consistency of findings across the cumulative body of evidence.

Fedak et al. state that the concept of *data integration* is inherently influential in the interpretation of the consistency criterion as it speaks to understanding a consistent story across multiple disciplines or practices.[29] In this case the statistically significantly increased risk of ovarian cancer associated with genital talc use seen in epidemiologic studies has continued to illustrate how consistently plausible biological mechanisms of development of ovarian cancer associated with perineal talc use provide can further support of epidemiologic findings, and likewise epidemiologic findings can be used to better

understand plausible biological mechanisms. Studies that provide evidence on the retrograde migration of talc,[13,14] are consistent with an increased risk seen in epidemiologic studies among women with patent reproductive tracts.[12,40] The findings that perineal talc use carries a higher risk among women with endometriosis compared to women without endometriosis as seen in the study by Phung et al.[5] provide further support for a biologically proposed mechanisms of inflammation as a pathway by which talc can increase the risk of ovarian cancer.[15]

Specificity. I placed less weight on absolute specificity of the association between talcum powder exposure and ovarian cancer given the multi-causal nature of the cancer outcome.

Temporality. In each of the epidemiologic studies noted above, talc exposure occurred before the diagnosis of ovarian cancer.

Biological Gradient. The presence of dose-response is not an absolute requirement for causation. While the presence of a dose-response relationship supports a causal link, the absence of such a relationship does not preclude a causal association. Hill acknowledged that more complex dose–response relationships may exist. Fedak et al., state that a monotonic dose–response curve is an overly simplistic representation of most causal relationships.[29] Most dose–response curves are non-linear depending on unique characteristics of population, exposure and outcomes.[29]

In order to determine dose-response, it is necessary first to determine dose which in this case represents the amount of cumulative talc exposure, the frequency of talc uses, and the duration of use. However, this was not consistently reported among the studies. It is important to note that a linear dose-response may not characterize the induction of ovarian cancer by talc, so it is difficult to adequately model dose-response relationships. Ascertaining a dose-response relationship with talc and ovarian cancer is particularly challenging given that the risk of ovarian cancer may vary with age, premenopausal and post-menopausal status, and the presence of other risk factors. The "*depletion of susceptibles*" over time may make it difficult to ascertain a dose-response relationship. As a result, some studies such as the study by Davis et al. did not find overall evidence of a dose-response trend.[8] Based on the above limitations with study design to ascertain dose effect, specificity of dosing of talc and the possibility of threshold effect, I find biological gradient less compelling, but there are some studies that provide evidence of a dose-response despite these challenges.

Taher et al.[11] identified five studies which provided evidence of a positive trend of an exposure response relationship and two studies concluded that there might be a exposure response.[18,39-44] When exposure measurements were standardized into talc years, they noted a possible increasing trend in ovarian cancer risk with increasing exposure to talc. The findings of Taher et al., were consistent with the meta-analysis conducted by Penninkilampi et al., which reported a higher risk among those with >3600 applications of talc (OR=1.42, 95% CI 1.25 to .61) compared to participants with <3600 applications, although with overlapping confidence intervals (OR=1.32, 95% CI 1.15 to 1.50).[1] Studies have also shown evidence of increased risk with increased number of lifetime applications, which may be a more accurate measure for long term exposure outcome association mediated via inflammation. [42]The overall higher magnitude of association between talc use and ovarian cancer seen in the meta-analysis by Woolen et al.,[3] which

evaluated frequent users compared to previous analysis among ever users, all of which reported a statistically significantly increased risk,[1,45,46] also provides some evidence of dose-response.

Taher et al. noted that the robust case-control study by Cramer et al. provided the strongest evidence of a dose-response based on categories of total genital applications.[18] Cramer et al. noted a significant trend for epithelial ovarian cancer risk and talc-years when nonusers are included.[18]Gabriel et al., also noted evidence of dose-response trend with increasing talc years (P_{trend}=0.0006).[9] Mills et al. found a dose–response by frequency of use.[40] Wu et al., looking at all types of body use, found a dose–response with estimated applications. Merritt et al., reported a significant trend in risk for invasive serous ovarian cancer with years of talc use.[54] Terry et al., reported no trend with increasing lifetime applications when restricted to talc users.[45] However, an increase in risk with increasing applications was found for nonmucinous epithelial ovarian cancer when nonusers were included. [45]

Plausibility. This viewpoint only requires biological mechanism to be *plausible*, which is necessarily limited to the state of biological knowledge at the time of assessment. Several new studies reported on biologically plausible mechanisms of genital talcum powder use and an increase in the risk of ovarian cancer.[13-17,20,33,34] These studies provide evidence on retrograde migration of talc particles,[13,14,16] promotion of inflammation,[13,17] and showed that talc particles, especially in the context of increased estrogen, impair the tumoricidal function of macrophages.[17] Studies show that that talcum powder can induce malignant transformation in normal human ovarian cell lines resulting in genetic changes further providing evidence of biologically plausible mechanisms of talc and an increased risk of ovarian cancer.[33,34]

The body of evidence based on retrograde migration and inflammation noted above meets the threshold of biological plausibility of genital talcum powder use and ovarian cancer. However, the FDA, Johnson & Johnson's testing, and the analyses of Drs. Longo and Rigler have documented the presence of asbestos in talcum powder products, an established cause of ovarian cancer,[19,20,21,22,23] which also provide another supportive biologically plausible mechanism of how genital talc use may cause ovarian cancer.

As a result of the significant body of evidence that has accumulated on biological mechanisms, I place significant weight on the fact biological plausibility provides evidence in support of the causal role of talc in the development of ovarian cancer and there is a highly biological plausible mechanism here for carcinogenicity which supports my opinion.

Coherence. This viewpoint assesses whether the cause-and-effect interpretation of data conflicts with the generally known facts of the natural history and biology of the disease. Multiple lines of epidemiological and biological evidence provide a coherent explanation that talcum powder products have biological effects which plausibly explain the occurrence of ovarian cancer. The biological mechanisms and causal association itself fit easily within the current framework of scientific knowledge about the development of ovarian cancer mediated by retrograde migration of talc and inflammatory mechanisms. I placed a significant weight on the coherence of findings in support of the causal role of talc in the development of ovarian cancer.

The epidemiologic evidence of an increased risk of ovarian cancer needs to be interpreted in the context of biology. Several new epidemiologic studies and studies on biological plausibility provide evidence in support of coherence. Recent epidemiologic studies have shown that there is an increase in the risk

among women with patent reproductive tracts,[12] in line with previous epidemiologic studies,[40] and studies on biological plausibility of how retrograde migration of tract and resulting inflammation can increase the risk of ovarian cancer. [13,14] Phung et al. also noted a statistically significantly risk of genital talc use and ovarian cancer in women both with and without endometriosis, with a higher risk among women with endometriosis than without endometriosis (OR 1.38 95% CI 1.04-1.84 vs. OR 1.12 95% CI 1.01-1.25). Endometriosis is known to be an inflammatory disease. These findings were consistent and coherent with the higher risk of ovarian cancer observed with talc use, because inflammation is one biological mechanism for the association between talc and ovarian cancer.[54]

Mandarino et al. reported that talc alone, and especially in combination with estradiol, introduced changes in gene expression that promoted a pro tumorigenic environment and less efficient tumoricidal activity of macrophages. The concentration of estrogen in ovarian tissue is more than 100-fold higher than in serum.[75] These findings explain why talc use is associated with ovarian cancer rather than at other sites. These findings are coherent with epidemiologic evidence that talc use was associated with an increased risk among pre-menopausal women and post-menopausal women who use hormone therapy.[18] The effect of interaction of the talc/ovarian cancer relationship may explain why the WHI which enrolled post-menopausal women, and evaluated hormone use as a confounder rather than effect modifier, failed to detect an effect between the use of genital talc and ovarian cancer.

Experiment. This overview is weighted as less important than the other more important viewpoints noted above because randomized controlled trials that evaluate the risk of ovarian cancer with talc use and non-use have not been performed and would likely be considered unethical.

Analogy. Asbestos has been shown to cause ovarian cancer which offers an appropriate analogy, but this viewpoint was considered less significant than other viewpoints noted above.

X. CONCLUSION

Based on my background, expertise, training and education as a physician and epidemiologist, review and analysis of the totality of the evidence, using the weight of evidence analysis, including considering and weighting the Hill viewpoints, as described in this report, it is my opinion stated to a reasonable degree of scientific and medical certainty that genital use of talcum powder products can cause ovarian cancer.

I reserve the right to review any new material that becomes available and update this report. I also reserve the right to review and comment on the expert reports and testimony of the Defendants' experts.

XI.REFERENCES

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		Include		Exclude						
		New Study	Previous Report	No Original Data	Non-Relevant	Opinion	Not Systematic Review or Meta-analysis	Not exposed to perineal Talc	Outcome Not Ovarian Cancer	Duplicate
1.	Al-Zoubi N, Partheniadis I, Aljaberi A, Nikolakakis I. Co-spray Drying Drugs with Aqueous Polymer Dispersions (APDs)—a Systematic Review. AAPS PharmSciTech 2022;23.							X		
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52.	Moline J, Patel K, Frank AL. Exposure to cosmetic talc and mesothelioma. J Occup Med Toxicol 2023;18.									X	
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80.	Salvador S, Scott S, Francis JA, Agrawal A, Giede C. No. 344 - Opportunistic salpingectomy and other methods of risk reduction for ovarian, fallopian tube, peritoneal cancer in the general population. J Obstet Gynaecol Can 2017;39:494-508.								X			
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Appendix B. A measurement tool for Assessment of Multiple Systematic Review (AMSTAR)(Shea, Hamel et al. 2009)			
	(Woolen, Lazar et al. 2022)	**(Kadry Taher, Farhat et al. 2019, Taher, Farhat et al. 2020)**	**(Lynch, Lauer et al. 2023)**
Criterion			
A priori design	Yes	Yes	Yes
Duplicate study selection & extraction	Yes	Yes	Yes
Comprehensive search	Yes	Yes	Yes
Status of publication used as criterion	Yes	Yes	No
List of included & excluded studies	No	No	No
Characteristics of studies provided	Yes	Yes	Yes
Scientific quality of studies addressed	Yes	Yes	Yes
Scientific quality of studies used in formulating. conclusions	Yes	Yes	Yes
Methods of combining studies appropriate	Yes	Yes	No
Likelihood of publication bias addressed	Yes	Yes	No
Conflict of interest included	Yes	Yes	Yes

Kadry Taher, M., N. Farhat, N. A. Karyakina, N. Shilnikova, S. Ramoju, C. A. Gravel, K. Krishnan, D. Mattison, S.-W. Wen and D. Krewski (2019). "Critical review of the association between perineal use of talc powder and risk of ovarian cancer." Reproductive Toxicology **90**: 88-101.

Lynch, H. N., D. J. Lauer, O. M. Leleck, R. D. Freid, J. Collins, K. Chen, W. J. Thompson, A. M. Ierardi, A. Urban, P. Boffetta and K. A. Mundt (2023). "Systematic review of the association between talc and female reproductive tract cancers." Front Toxicol **5**: 1157761.

Shea, B. J., C. Hamel, G. A. Wells, L. M. Bouter, E. Kristjansson, J. Grimshaw, D. A. Henry and M. Boers (2009). "AMSTAR is a reliable and valid measurement tool to assess the thodological quality of systematic reviews." J Clin Epidemiol **62**(10): 1013-1020.

Taher, M. K., N. Farhat, N. A. Karyakina, N. Shilnikova, S. Ramoju, C. A. Gravel, K. Krishnan, D. Mattison, S. W. Wen and D. Krewski (2020). "Data on systematic review and meta-analysis of epidemiologic evidence on the association between perineal use of talc powder and risk of ovarian cancer." Data Brief **29**: 105277.

Woolen, S. A., A. A. Lazar and R. Smith-Bindman (2022). "Association Between the Frequent Use of Perineal Talcum Powder Products and Ovarian Cancer: a Systematic Review and Meta-analysis." J Gen Intern Med **37**(10): 2526-2532.

EXHIBIT A

Sonal Singh MD MPH FACP

Associate Professor
UMass Chan Medical School
Tel: (336)-473-1604
sonal.singh@umassmemorial.org

Education

MPH, Bloomberg School of Public Health, Johns Hopkins University
Baltimore, MD 6/2005 to 5/2008

Internal Medicine Residency, Unity Health System, affiliate University of Rochester
Sch of Medicine and Dentistry, Rochester, NY 7/2002 to 6/2005

MD, Patna Medical College, Patna, India 12/91 to 05/1999

Academic Appointments

Associate Professor, Department of Family Medicine & Comm Health 10/2016 to date
Department of Medicine, University of Massachusetts Medical School

Assistant Professor, Dept of Medicine, Johns Hopkins Univ SOM 7/2009 to 9/2016

Assistant Professor, Center for Public Health, and Human Rights
Bloomberg School of Public Health, JHU 7/2009 to 9/2016

Assistant Professor, Department of Medicine, Wake Forest University 7/2007 to 6/2009

Instructor, Department of Medicine, Wake Forest University 7/2005 to 06/2007

Employment History

Associate Professor, Department of Fam Medicine & Comm Hlth 10/2016-present
UMass Chan Medical School
Role: Clinician- Investigator

Associate Professor, Department of Quantitative Health Sciences 10/2018-present
UMass Chan Medical School
Role: Clinician- Investigator

Associate Professor, Department of Medicine, Division of Hlth System Sciences 10/2022-present
UMass Chan Medical School
Role: Clinician- Investigator

Assistant Professor, Dept of Medicine, Johns Hopkins University. 7/2009 to 9/2016
Role: Clinician- Investigator

Assistant Professor, Department of Medicine, Wake Forest University 7/2007 to 6/2009

Role: Clinician- Educator

Instructor, Department of Medicine, Wake Forest University 7/2005 to 6/2007
Role: Clinician- Educator

Residency (Medicine) Unity Healthy System, University of Rochester, Rochester, NY Role: PGY 1, PGYII and PGY III Internal Medicine Resident 7/2002 to 6/2005

Research Associate, Clinical Pharmacology, Ohio State University 3/2001 to 6/2002
Role: Research assistant in clinical trials

Voluntary Research Associate, Clinical Pharmacology, Ohio State 8/2000 to 2/2001
Role: Research assistant in clinical trials

USMLE STEP 1, II, III and Clinical Skills Exam Preparation 2/2000 to 7/2000
Role; Medical student

Resident, Medicine, Patna Medical College, Patna, Bihar, India 2/1998 to 1/2000
Role: Junior Resident in Medicine

Compulsory rotatory internship, Patna Medical College, Patna, India 12/1997 to 12/1998
Role: Fulfilling requirements for completion of medical degree in India

Certification and Licensure

Diplomate, American Board of Internal Medicine	8/2005-12/2025
Massachusetts Board of Physicians	8/6/2016-8/6/2023
Physicians and Surgeons of Maryland (Inactive)	2009-2017
North Carolina Medical Board (Inactive)	2005-2009
Basic Life Support (Active)	2016-2023

Professional Memberships and Activities

Massachusetts Medical Society	2017-current
American College of Physicians	2003-current
International Society of Pharmacoepidemiology	2011-current
Society of General Internal Medicine	2003-2016
International Society of Pharmacoeconomic Outcomes Research	2016-2017
Academy Health	2013
Global Health Council	2006-2010
Association of Physicians of Indian Origin (AAPI)	2020-current

Honors and Awards

- 2022 : Dave Sackett Clinical Trial of the Year Award, Society for Clinical Trials, Member, Data Safety Monitoring Committee-TOGETHER trial

- 2019: Elected to the Fellow of the American College of Physicians
- 2017 : Elected, American College of Chest Physicians CHEST Expert Cough Panel
- 2016: Finalist W. Leigh Thompson Excellence in Research: Johns Hopkins University SOM
- 2013 : Visiting Professor, Department of Medicine, University of Alabama, Alabama, USA
- 2013 : Appointee World Health Organization, International Agency for Research on Cancer Evaluation of Drugs and Herbal Products, Lyon, France.
- 2013 : Awardee, 29th International Society of Pharmacoepidemiology, Montreal, IIIrd Best Abstract, Trainee
- 2011 : Awardee, Bruce P Squires Award for the Best Research Paper, Canadian Medical Association Journal
- 2011:Awardee, Society of General Internal Medicine Clinical Investigator (Mid-Atlantic)
- 2010 : Awardee, Scholars Abstract Award, Society for Clinical and Translational Sciences
- 2009 : Awardee, NIH/KL2 Award and Junior Research Scholar, Johns Hopkins Clinical Research Program, Johns Hopkins School of Medicine
- 2010 : Elected, Delta Omega Honorary Public Health Society, Johns Hopkins University
  2008 : Elected Master Teacher Award, Wake Forest University School of Medicine
- 2006 : Awardee, Tinsley R Harrison Faculty Teaching Award Wake Forest University SOM
- 2007 : Awardee, Tinsley R Harrison Faculty Teaching Award Wake Forest University SOM
- 2005 : Senior–Resident Scholarship award, Unity Health System, University of Rochester SOM& Dentistry
- 2005 : American College of Physicians Health and Public Policy Scholarship, NY

Committee Assignments & Administrative Service

Public Policy Committee, International Society of Pharmacoepidemiology	2020-2021
Population Health & Pharmacy Collaborative Committee, UMASS	2019-2020
American College of Physicians, Massachusetts, Health Policy Committee	2018-2019
Chairs Advisory Council, Department of Fam Medicine & Comm Hlth	2016-2018
American College of Chest Physicians, Cough Guideline Expert Panel	2017- current
Associate faculty, Welch Ctr for Prevention, Epi & Clin Research, JHU	2015-2016
Associate-Director, Center for Drug Safety and Effectiveness, JHU	2013-2016
Affiliate faculty, Center for Hlth Services and Outcomes Research, JHSPH	2012-2016
WHO, International Agency of Research on Cancer (IARC) Working group	2013
Preferred Items for Reporting of Systematic Reviews and Meta-analysis of harms Working Group Alberta Canada.	2012-2012
Health & Human Rights Working Group, JHU Center for Aids Research	2012
Core faculty, Center for Public Health and Human Rights, Johns Hopkins Bloomberg School of Public Health	2009-2016
Core faculty, Evidence-Based Practice Center, JHU	2009-2016
Medical Director, Outpatient Clinic, WFUSOM	7/2005-6/2009

Teaching Activities

Classroom

Epidemiology 2020-2022
Role: Facilitator course in Clinical Epidemiology for Medical Students at University of Massachusetts Medical School

Comparative effectiveness research (2 credits), Johns Hopkins Medicine 2015-2016
Role: Developed course in CER for MD and MD/PhD trainees in the CTSA

Health and Human Rights, Johns Hopkins Bloomberg School of Public Health 2011-2015
Role: Annual lecture in the course for MPH students

Health Economic, Johns Hopkins Bloomberg School of Public Health 2013
Role: Annual lecture in the course for master's students

Pharmacoepidemiology, Johns Hopkins Bloomberg School of Public Health 2011-2015
Role: Annual lecture in the course for master's and Doctoral students

Evidence-based Medicine, Johns Hopkins University School of Medicine 2012
Role: Course facilitator

Intro to Clinical Investigation, Johns Hopkins University School of Medicine 2012
Role: Annual lecture in the course

Clinical Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2010-2014
Role: Annual lecture in the course

Patient Physician and Society, Johns Hopkins University School of Medicine 2009
Role: Course facilitator

Clinical Teaching

Outpatient medicine 2016-current
Role: Precepting IIIrd year medical students in clinic at University of Massachusetts Medical School
Evidence Based Medicine 2012-2014

Role: Developed a novel course to teach Evidence based Medicine to Osler medical residents at Johns Hopkins University School of Medicine
Outpatient medicine 2005-2009

Role: Precepting residents in clinic at Wake Forest University
Inpatient Medicine 2005-2009
Role: Precepting internal medicine residents at Wake Forest University

Mentoring

UMass Chan Medical School		Project	Current Position and Institution	Training Period
Faculty				
Idanis Berriosmorales MD	Mentor	SR of SDM in MS	Asst. Professor of Neurology, UMass Chan Medical School	2019-2021
Mayuko Itofukunaga, MD	Mentor	Systematic review of decision aids for lung cancer screening	Assistant Professor-Pulmonary Medicine UMass Chan Medical School	2018-2020
Ayobami Akenroy MD	Mentor	Pharmacovigilance study of switching biologics in asthma	Assistant Professor-Harvard Medical School	2022
Trainees				
Jessica Kloppenburg	Scholarly activity	SR of SARS-COV-19 and Maternal-fetal outcomes	MD/PhD Student UMass Chan Medical School	2020-
Nathaniel, Erskine MD, PhD (student)	Scholarly activity	SR of herpes zoster and cardiovascular disease	MD/PhD Student UMass Chan Medical School	2017-18
Richeek Pradhan MS	Scholarly Activity	Comparison of data on Adverse events	Post-doctoral Fellow, Harvard School of Public Health	2017-18
Johns Hopkins University				
Faculty				
Hsien-Yen Chang PhD	Mentor	Pharmacoepidemiologic studies	Director, Real World Research at Jannsen LLC	2011-15
Trainees at Johns Hopkins Bloomberg School of Public Health				
Omar Mansour	Scholarly activity	SGLT2inhibitors and cardiovascular outcomes	Masters' student, JHSPH	2018
Geetha Iyer, MD	Mentor	Multiple Pharmacoepidemiologic studies	Post-doctoral fellow, Harvard School of Public Health	2015-16

Sathiya Priya Marimathu, MPH	Mentor	Generic drugs and patient-oriented outcomes	Senior Clinical Trial Physician at Bristol Myers Squibb	2015-16
Yohalakshmi Chelludari, MD, MPH	RA Scholarly activity	Review of varenicline	Internist, Salem, Oregon	2013
Hasan Shihab, MD, MPH	Scholarly activity	Review of GLP-based therapies	Attending Physician OSF HealthCare, IL	2013-14
Joshua Sclar, MD, MPH	Scholarly activity	Systematic review of attacks on health workers	Chief Medical Officer, Avesis	2013
Crystal Ng, MPH	Scholarly activity	Human Rights measures	MPH Student, JHSPH	2013
Ekta Agarwal, MPH	Capstone	Safety of novel anticoagulants	Senior Director/ Evidence Generation Lead/ Pfizer	2013
Meijia Zhou, MHS	Scholarly activity	Adherence to novel anticoagulants	Manager, Real-World Data Analytics & Research, Medical Devices Epidemiology, Johnson and Johnson	2013
Kaitlin Hayman, MD	Capstone	SR of the impact of disasters On CVD outcomes	MPH student, JHSPH	2013
Wenze Tang, MPH	Scholarly activity	SCCS analysis of GIB bleeding with dabigatran	Manager, Janssen Pharmaceutical Companies of Johnson & Johnson	2013
Shabana Walia MD	Scholarly activity	SR of CVD among refugees and displaced	ER physician, UT Houston	2016-18
Wake Forest University SOM				
Aman Amin, MD	Scholarly activity	SR of Inhaled corticosteroids and pneumonia	Practicing internist, NC	2007-09
Apurva Trivedi, MD	Scholarly activity	Systematic Review of SSRIs and bleeding	Gastroenterologist	2007-09
External institutions				
Tonya Breaux-Shropshire PhD, MPH	Scholarly activity	Systematic review of ambulatory BP	Clinical Scientist in Hypertension Research at University of Alabama at Birmingham	2015
Abhay Kumar, MD	Resident Scholarly activity	Wernicke encephalopathy after gastric bypass: systematic review	Associate Professor of Neurosurgery, UT Houston	2007

Submitted Grants
NIA (NOT-AG-23-032) (PI : Gurwitz) 09/22-04/2024 Developing Processes and Tools to Assess the Safety of Antiamyloid therapies for Alzheimer's Disease using Real World Data. The aim is to develop tools to assess the safety of anti-amyloid therapies for Alzheimer's Disease using Real World Data Role (Co-investigator 10% FTE)
Current Grants
Developing and applying a framework to evaluate and conduct algorithm validation studies for MACE 11/2023- 10/2024. Reagan Udall Foundation for the FDA $ 130,000 The aim is to develop the Algorithm Certainty Tool (ACE-IT) tool to appraise whether real world algorithms are fit for purpose for regulatory surveillance with a focus on major adverse cardiovascular outcomes
1 R01 MD016883-01 (PI-Fisher) 5/17/21-02/29/2024 NIMHHD $702,150 Trusted messengers: Supporting physicians in promoting COVID-19 vaccination. The major goals of this project are: (1) To refine and adapt tools to support effective PCP recommendations for COVID-19 vaccination and information dissemination by PCPs and community organizations to vulnerable patients; (2) To implement and assess the impact of the intervention on COVID-19 vaccine uptake among initially unvaccinated patients and (3) To evaluate the intervention according to the REAIM framework, incorporating the perspectives of patients, primary care providers, and clinic leaders. Role: Co-Investigator (15%)
NIH 33AG069794 9 (PI-Gurwitz) 09/2021-08/2025 Developing a Program to Educate and Sensitize Caregivers to Reduce the Inappropriate Prescription Burden in Elderly with Alzheimer's Disease Study (D-PRESCRIBE-AD) 1,077,838 (FY23) The aim is to conduct a large, cluster randomized, pragmatic trial to evaluate a health plan-based intervention leveraging the NIH Collaboratory's Distributed Research Network, which uses the Food and Drug Administration (FDA) Sentinel Initiative infrastructure. Role: Co-investigator (20%)
Completed Grants and Contracts
NIA 3R33AG057806-05S1 09/22-04/2024 Preparing for what is next with aducanumab in Real World Settings (PI-Gurwitz) NIA $ 434,125 The aim is to develop a state-of-the-art master protocol to conduct a real-world evaluation of the novel monoclonal antibodies for dementia. Role (Co-investigator 20% FTE)
Developing and applying a framework to evaluate and conduct algorithm validation studies for MACE 03/2021—5/2022. Reagan Udall Foundation for the FDA $ 105,462 The aim is to develop the Algorithm Certainty Tool (ACE-IT) tool to appraise whether real world algorithms are fit for purpose for regulatory surveillance with a focus on major adverse cardiovascular outcomes. Role : Principal Investigator (15%)

NIH R61AG069794-01(PI-Gurwitz) 09/2020-08/2021 Developing a Program to Educate and Sensitize Caregivers to Reduce the Inappropriate Prescription Burden in Elderly with Alzheimer's Disease Study (D-PRESCRIBE-AD) The aim is to conduct a pilot study to assess the feasibility and acceptability of a large, cluster randomized, pragmatic trial to evaluate a health plan-based intervention leveraging the NIH Collaboratory's Distributed Research Network, which uses the Food and Drug Administration (FDA) Sentinel Initiative infrastructure. Role: Co-investigator- 15%
PCORI HIS-1608-35689-IC (PI-Ming Tai-Seale) 2/2016- 3/2021 Improving Patient-Centered Communication in Primary Care: A Cluster Randomized Controlled Trial of the Comparative Effectiveness of Three Interventions The aim is to compare three interventions to improve patient communication in primary care. Role: Co-investigator (10%)
(PI Jerry Gurwitz) 08/2018- 08/2020 NIH/NIA-1 R56 AG061813-01 Project Title: Controlling and Stopping Cascades leading to Adverse Drug Effects Study in Alzheimer's Disease(CASCADES-AD) Role: co-investigator. The aim is to develop interventions to prevent prescribing cascades among those with Alzheimer's related Dementia (ADRD)
Death Data Exploration 08/01/17- 03/02/18 Task Order Number: HHSF22301012T Efforts to Develop the Sentinel Initiative HHSF223200910006I. Role (Project Lead)
Effect of Therapeutic Class on Generic Drug Substitutions. 2014-2016 U01FD005267-01 (PI, Jodi Segal) FDA $ 349,480 Role: Co-Investigator
Comparative effectiveness Research & The Cochrane Eyes and Vision Group 2013-16 U01 EY020522 (PI, Kay Dickersin) NIH/NEI $ 825,397 Role: Co-Investigator
Systematic review of gabapentin for neuropathic pain using multiple data sources 2015-16 (PI, Caleb Alexander) FDA Center of Excellence in Regulatory Science Role: Co-Investigator (20% effort)
Integrating multiple data sources for meta-analysis to improve patient-centered outcomes. research 2014-2016 (PI- Dickersin) PCORI (ME-1303-5785) $698,174 Role: Advisor (2% effort)
Development of a scale for human rights violations. 2013-2014 (PI, Chaisson & Beyrer) NIH Johns Hopkins Center for AIDS Research $ 18,873 Role: Pilot Awardee

Comparative effectiveness review of therapeutic options for obesity in the Medicare population. Johns Hopkins Evidence Based Practice Center. 2013-2014 PI (Eric Bass) AHRQ $125,000 Role: Co- Investigator (20% effort)	
Center for Excellence in Comparative Effectiveness Education PHRMA Foundation (PI Jodi Segal) Role: Co-investigator (5% effort)	2012-2013 $250,000
A multi criteria decision analysis to assist with regulatory decisions around benefit and risk. Partnership in Applied Comparative Effectiveness Science: PI (PI, Jodi Segal). FDA Role: Project Principal Investigator (25% effort)	2010-2013 $3,509,657
Combination therapy vs. intensification of statin monotherapy: An update. PI (E. Bass- P.I of EPC.) AHRQ Role: Advisor (5% effort)	2012-2013
Troponin cardiac marker during renal impairment. (E. Bass- P.I of EPC.) Agency for Health Care Quality and Research Role: Advisor (5% effort)	2012-2013
To develop an instrument for attacks on health workers. PI (Len Rubenstein) US Institute of Peace Role: Co-investigator (10% effort)	2012-2013
To develop an instrument for attacks on health workers. PI (Len Rubenstein) McArthur Foundation Role: Co-investigator (15% effort)	2012-2013 $434,782
To conduct a benefit and harm assessment of *roflumilast* in COPD. Johns Hopkins ICTR Role: Co-investigator (5% effort)	2012-2013
To develop a China-JHU consultation for civil society public health professionals. Open Society Foundation Role: PI (20% effort). Proposal for a public health training program.	2012 $49,534
PACER. PI (Rothman) Google-Flu Role: Coinvestigator (5%) Systematic reviewer and meta-analysis expert.	2012
Methods for Balancing Benefits and Harms in Systematic Reviews Johns Hopkins Evidence Based Practice Center. (PI, Bass) AHRQ Role: Project Task Leader and co-Investigator (10% effort)	2011-2012 $188,871

Comparative effectiveness review of Meditation Programs for Stress and Wellbeing Johns Hopkins Evidence Based Practice Center. (PI, Bass) AHRQ Role: Project Task Leader and co-Investigator (15% effort)	2011-2012 $375,666
Comparative effectiveness review of prevention of VTE in special populations Johns Hopkins Evidence Based Practice Center. (PI, Bass) AHRQ Role: Project Principal Investigator (20% effort)	2011-2012 $375,666
To prevent and respond to gender-based violence (GBV) in refugee and conflict-affected populations. (PI, Vu & Rubenstein) Role: Co-investigator (10% effort)	2010-2011 $293,946
Comparative effectiveness review of oral hypoglycemic medications Johns Hopkins Evidence Based Practice Center. (PI, Bass) AHRQ Role: Co- Investigator (0% effort)	2009-2010 $125,000
Johns Hopkins Clinical Research Junior Faculty Award. NIH-KL2 ICTR Role: Recipient (75% salary support)	2009-2012
Measuring exposure to human rights violations among men who have sex with men. (PI, Mullany). Center for Global Health Johns Hopkins Role: Co-investigator (0% effort).	2009-2010 $50,000.00
Research ethics for conducting research in vulnerable populations and unstable settings. (PI, Mills) CIHR Role: Co-investigator (10% effort).	2007-2009 $99, 887.00

Editorial work

Editor-in-chief and founder

BMC Conflict and Health 2017-2012

Editorial Board Membership

Frontiers in Drug Safety	2022-current
Frontiers in Primary Care and Family Medicine	2021 current
Evidence Based Medicine (BMJ Group of Journals)	2017- 2023
Drug Safety	2008-2016
American College of Physicians	PIER

Grant Review

Extramural Grant Review for US Federal Agencies
Center for Disease Control. Special Emphasis Panel Effective Community Conversations for Influenza and COVID-19 Vaccine Uptake May 2 2023
Patient Centered Outcomes Research Institute- Rare Disease Research Panel, November 20, 2020
International Agencies
Medical Research foundation of New Zealand
Medical Research Council of South Africa
Catalina Health Technology Assessment, Spain
Diabetes, UK
Intramural
Johns Hopkins Center for Public Health and Human Rights Junior Faculty Research Grants
Johns Hopkins Medicine Research Council Synergy Awards
Johns Hopkins Institute for Clinical and Translational Research Awards

Data Safety Monitoring Board

Repurposed Approved Therapies for Outpatient Treatment of Patients with Early-Onset COVID-19 and Mild Symptoms (www.togethertrial.com) David Sacket Clinical Trial of the Year Award 03/2021

Peer Review

Acta Diabetologica
American Heart Journal
American Journal of Addictions
American Journal of Cardiovascular Drugs
American Journal of Managed Care
American Journal of Psychiatry
American Journal of Tropical Medicine and Hygiene
Annals of Internal Medicine
Annals of Medicine
Australian Medical Journal
BMJ
BMC Clinical Pharmacology
British Journal of Clinical Pharmacology
Bulletin of the World Health Organization
Chest
Circulation
Canadian Medical Association Journal
Clinical Pharmacology and Therapeutics
Clinical Trials
Cardiovascular Drugs & Therapy
Cochrane Collaboration
Disasters
Diabetolgia
Drug and Alcohol Dependence
Diabetes Obesity and Metabolism
Drug Safety
Epidemiology
European Journal of Neurology
European Journal of Pharmacology
European Respiratory Journal
Expert Opinion in Drug Safety
Global Public Health
Health Policy
International Journal of Clinical practice
International Journal of Epi
International Journal of Obesity
Journal of the American College of Cardiology
Journal of the American Medical Association > 25 articles
Journal of the American Medical Association-Internal Medicine
JAMA-Network Open
Journal of Cardiac Failure
Journal of Medical Case Reports
Journal of the Pancreas
Journal of General Internal Medicine
Medscape General Medicine
Medical Journal of Australia

. *Nephrology Dialysis Transplantation*
. *North Carolina Medical Journal*
. *Nutrition, Metabolism & Cardiovascular Diseases*
. *Open Forum for Infectious Disease*
. *Pediatric Infectious Disease Journal*
. *Pharmacoepidemiology & Drug Safety-Best Reviewer Award 2013*
. *Public Library of Science Medicine*
. *Primary Care Respiratory Journal*
. *Pediatrics*
. *Research Synthesis Methods*
. *Respiratory Medicine*
. *Respirology*
. *Southern Medical Journal*
. *The Lancet*
. *Thorax*
. *Tropical Medicine & International Health*

ABSTRACTS/PRESENTATIONS

National/International Oral Conference Presentation

1. Mazor KM, Fisher KA, Nguyen N, Fouayzi H, Crawford S, Singh S, Dong M, Wittenberg R. From vaccine hesitancy to vaccine acceptance: Who changes and why? Oral presentation at: The Health Care Systems Research Network; April 12-14, 2022; Pasadena, CA.
2. Risk of myocarditis associated with checkpoint inhibitors. 35th International Society of Pharmacoepidemiology, Annual Meeting, Philadelphia. Aug 26, 2019.
3. GLP-1-based therapies and risk of pancreatitis: A matched case-control study. 29th International Society of Pharmacoepidemiology, Annual Meeting, Montreal Convention Center, August 26. Montreal, Quebec, Canada.2013
4. GLP-1 based therapies and risk of pancreatitis. 36th SGIM Annual Meeting, Denver, Colorado. 2013
5. Risk of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of randomized controlled trials and observational studies, Society of General Internal Medicine, Minneapolis, Minnesota. 2011
6. Odds of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of clinical trials and observational studies, 27th International Society of Pharmacoepidemiology, Annual Meeting, Hyatt Regency August 24th. Chicago, Illinois. 2011

National/International Poster Presentation

1. Suad Khabbaha, Sarah Carder Dempsey, Aranka Anema, Sonal Singh, and Kristian Thorlund. Characterizing adverse events across 30,000 peer reviewed case report publications. Journal of Clinical Oncology 2023 41:16_suppl, e18858-e18858. Published online May 31 2023. 2023 ASCO Annual Meeting.
2. Suad Khabbaha, Sarah Carder Dempsey, Aranka Anema, Sonal Singh, and Kristian Thorlund. Is aggregate use of published case reports as a viable option for augmenting pharmacovigilance? An applied example of pembrolizumab-related adverse events in patients with non-small cell lung

cancer receiving first-line treatment. Journal of Clinical Oncology 2023 41:16_suppl, e18840-e18840. Published online May 31 2023. 2023 ASCO Annual Meeting.

3. Sonal Singh, Julie Beyrer, Xiaofeng Zhou, Joel N Swerdel, Raymond A Harvey, Kenneth Hornbuckle, Leo Russo, Kanwal Ghauri, Ivan H Abi-Elias, Carla V Rodriguez-Watson. Development and Evaluation of the ALgorithm CErtainty Tool KIT (ACE-IT) to evaluate safety outcomes using electronic medical record and claims-based algorithms. 38th International Society of Pharmacoepidemiology, Annual Meeting, Copenhagen, Denmark. Aug 28, 2022.
4. Thomas Moore, Sonal Singh. Challenges of Using Real-World Evidence for Regulatory Decisions: 4 Key Issues. 38th International Society of Pharmacoepidemiology, Annual Meeting, Copenhagen, Denmark. Aug 27, 2022.
5. Sonal Singh. Noelle Cocoros, Kevin Haynes, Vinit Nair, Thomas Harkins, Paula Rochon, Richard Platt, Sybil Crawford, and Jerry Gurwitz. Population based estimates of prescribing cascades among older adults with Alzheimer's dementia. 36th International Society of Pharmacoepidemiology, Annual Meeting. September 16th 2020
6. Sarah Bloomstone KA, Noelle Cocoros,Jerry Gurwitz,Kevin Haynes,Vinit Nair, Richard Platt,Paula Rochon,Sonal Singh, Kathleen M. Mazor. Prescribing Cascades in Patients With Alzheimer's Disease: Engaging Patients, Caregivers, Payers, and Providers. Abstracts from the 26th annual Health Care Systems Research Network Conference, April 8-10, 2020. J Patient Cent Res Rev. 2020;7:94.
7. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review 2018. International Society of Pharmacoepidemiology, Prague, August 24, 2018.
8. Risk of gastrointestinal bleeding among dabigatran users-a self-controlled case series analysis. Health Care Systems Research Network, San Diego, March 22, 2017.
9. GLP-1 based therapies and risk of pancreatitis. Pancreatitis, Diabetes, and Pancreatic Cancer Workshop. NIH, Bethesda, Maryland. 2013
10. Thiazolidinediones and risk of bladder cancer: A systematic review and meta-analysis. 36th SGIM Annual Meeting, Denver, Colorado.2013
11. Who is the patient's doctor? Primary care responsibility and co-management relationships among generalist and non-generalist physicians in the National Ambulatory Care Survey, 2002 SGIM 29th Annual Meeting, Los Angeles, California.2006
12. The educational value of case reports from the SGIM national meeting in the internal medicine clerkship. SGIM 29th Annual Meeting, Los Angeles, California.2006
13. Using iPod technology to create a self-guided clinic tour for resident orientation SGIM 29th Annual Meeting, Los Angeles, California.2006
14. Narcotic management in chronic non-malignant pain. A survey of residents' knowledge and attitudes. SGIM 29th Annual Meeting, Los Angeles, California.2006
15. Formulary conversion programs pose a significant risk to patients, SGIM 27th Annual Meeting, Chicago, Illinois.2004

Posters at local regional meetings

Inhaled corticosteroids and the risk of fractures in COPD: A systematic review and meta-analysis. DOM Annual retreat, Johns Hopkins University 2011

National/International Oral Presentations

1. Development and Evaluation of the ALgorithm CErtainty Tool KIT (ACE-IT) to evaluate safety outcomes using electronic medical record and claims-based algorithm. International Society of Pharmacovigilance (ISoP) Journal Club. Webinar March 30 2023
2. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. NIH Collaboratory Grand Rounds. March 2, 2018
3. Resurgence of hepatocellular carcinoma in the era of oral direct acting antivirals. Cause or Consequence? Fundamentals of Biomedicine Seminar Series. Texas Tech University Health Sciences Center. El Paso, Texas Dec 13, 2017
4. Aligning evidence with preferences: Methodological Challenges and Opportunities Dartmouth-Hitchcock Medical Center, Dartmouth, New Hampshire, June 15, 2016
5. Aligning evidence with preferences: Methodological Challenges and Opportunities Department of Health Services and Research, Michael De-Bakey VA and Baylor University, Houston, Texas, May 16, 2016.
6. Aligning evidence with preferences: Methodological Challenges and Opportunities Meyers Primary Care Institute and Department of Family and Community Medicine, University of Massachusetts, Massachusetts, March 31 and June 9, 2016.
7. Aligning evidence with preferences: Methodological Challenges and Opportunities VA Center for Chronic Disease and Outcomes Research, Minnesota VA, March 2016.
8. Aligning evidence with preferences: Methodological Challenges and Opportunities Department of Medicine. University of Central Florida, Orlando, Florida, November 2015.
9. Aligning evidence with preferences: Methodological Challenges and Opportunities Center for Health Policy and Research Grand Rounds. UC Davis, Sacramento California, Oct 9, 2015.
10. Aligning evidence with preferences: Methodological Challenges and Opportunities Center for Evidence and Outcomes, Agency for Health Care Research and Quality. Gaithersville Maryland, August 31, 2015.
11. Risks of Spiriva Respimat outweigh its benefit: A Debate. Inhalation Asia, University of Hong Kong, Department of Pharmacology and Pharmacy, Hong Kong. 2013
12. GLP-1-based therapies and risk of pancreatitis. Center for Clinical Epidemiology and Biostatistics Seminar Series, University of Pennsylvania Philadelphia, Pennsylvania. 2013
13. Visiting Professor. Department of Medicine. University of Alabama. 2013
14. Value based health care: Can shared decision making methods get us there? Center for Value and Effectiveness, Medicine Institute, Cleveland Clinic, Noon Conference.2013
15. Role of Multi-criteria decision analysis in regulatory policy. Stanford Prevention Research Center, Stanford University, Palo Alto, Stanford, California. 2013
16. Role of Multi-criteria decision analysis in regulatory policy. South Carolina College of Pharmacy, Columbia, South Carolina.2013
17. Role of Multi-criteria decision analysis in regulatory policy. Department of Medicine. UC Davis, Sacramento, California.2013
18. Role of Multi-criteria decision analysis in regulatory policy. Department of Clinical Sciences, UT Southwestern, Dallas, Texas.2013
19. Role of Multi-criteria decision analysis in regulatory policy. Department of Medicine, Geisinger Medical Center, Danville, Pennsylvania. 2013

20. Weighing benefits and risks: Role of shared decision making in type 2 diabetes. CTSA Grand Rounds, Mayo Clinic, Rochester, Minnesota. 2013
21. Are long-acting muscarinic agents safe for patients with COPD: A Debate. Airway Vista, Asan Medical Center, Seoul, Korea
22. Academia and industry collaboration for cardiovascular risk mitigation. CBI and Applied Clinical Trials. 6th Annual Summit, Closing Address. Ritz Carlton, Arlington, Virginia.2012
23. Varenicline: Where are we today? Tobacco Disease Research Program, UCSF. San Francisco California. Varenicline debate.2012
24. The Maoist Insurgency in Nepal: Health Systems Challenges and Opportunities Conference on Health in Fragile States: Challenges for the Next Decade. United States Institute of Peace. Washington DC.2011
25. Standards of Care and the Role of Community Advocacy in Clinical Trials. Clinical Research in Developing Countries, Third Annual Marcus Evans Conference, Washington, DC.2008
26. Nepal-A Case study. Integrating public health methods into Conflict Analysis. Norman Patterson School of International Affairs, Carleton University, Ottawa, Canada.2007

Local/Regional Presentations

1. Development and Evaluation of the ALgorithm CErtainty Tool KIT (ACE-IT) to evaluate safety outcomes using electronic medical record and claims-based algorithm. Department of Family Medicine and Community Health 2023. Monthly Research Forum. January 20, 2023.
2. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. Research Seminar Series, Department of Family Medicine, and Community Health. University of Massachusetts Medical School. June 15. 2018
3. Safety of novel anticoagulants vs warfarin- a case study using complementary study designs. Quantitative Health Sciences, University of Massachusetts Medical School, February 28, 2017
4. GLP-1-based therapies and risk of pancreatic adverse events. University of Maryland, Division of Endocrinology, Metabolism and Nutrition, Grand Rounds, Baltimore, Maryland. 2013
5. Thiazolidinediones and Patient-Oriented Outcomes in Type 2 Diabetes, GIM Grand Rounds. Johns Hopkins University School of Medicine. 2012
6. Patient-Centered Benefit and Risk Assessment. Center for Health Services and Outcomes Research. Johns Hopkins University 2012
7. Varenicline and cardiovascular and neuropsychiatric adverse events: Do benefits outweigh risks? Welch Center Grand Rounds. Johns Hopkins University. 2011
8. The new wave, HIV, Human Rights and Men who have Sex with Men in Nepal. Johns Hopkins Bloomberg School of Public Health, 2011.
9. Network Meta-analysis and Serious Adverse Events. Network Meta-Analysis Methods Workshop. Johns Hopkins Bloomberg School of Public Health. 2010
10. Thiazolidinediones and Cardiovascular Outcomes in Type 2 Diabetes. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2008
11. How Safe Are Our Drugs and How Do We Know? North Carolina ACP, Durham.2008
12. Clinical Pathologic Conference. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007

13. Globalization and Health Equity: An emerging Challenge for Academic Medicine. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007
14. Thiazolidinediones and Cardiovascular Disease: The Seduction of Common Sense. Epidemiology Seminar Series, Public Health Sciences. Wake Forest University 2007

National/International Workshops

1. ICPE International Meeting Copenhagen, Denmark, Copenhagen. Safety of antidiabetic medication oral presentation (Moderator). August 28, 2022
2. M Hernan, T Wilke, EJ Mills, S Singh Head-to-head comparisons of therapies using real world data: What is needed to emulate target trials. ICPE Virtual meeting 2020 (Panelist)
3. Ulka Campbell, Sengwi Kim, Sengwee Toh, Seamus Kent, Jeffrey Brown, Sonal Singh, Carla Rodriguez-Watson. What Do Real World Data Validation Best Practices Look Like? Operationalizing Guidance for Real World Studies intended for Decision-Making. 38th International Society of Pharmacoepidemiology, Annual Meeting, Copenhagen, Denmark. Aug 28, 2022. (Panelist)
4. ISPOR National Meeting. Head-to-Head Comparisons using Real World Data (RWD): Is the era of network of meta-analysis over. [Moderator and Chair] Virtual Meeting. May 18, 2020
5. ISPOR National Meeting, Next Generation Comparative Effectiveness Research- Are we getting organized to facilitate research for the individual patient? Washington, DC May 24, 2016 (workshop)
6. SGIM national meeting, developing high-quality search strategies for systematic reviews. 2010
7. SGIM national meeting, Systematic Review. 2009

Peer reviewed Original Research Publications

Mentees *
Lead methodologist **

1. Cocoros NM, Gurwitz JH, Cziraky MJ, Granger CB, Harkins T, Haynes K, Li X, Parlett L, Seeger JD, **Singh S**, McMahill-Walraven CN, Platt R. Pragmatic guidance for embedding pragmatic clinical trials in health plans: Large simple trials aren't so simple. Clin Trials. 2023 Jun 15:17407745231160459. doi: 10.1177/17407745231160459. Epub ahead of print. PMID: 37322894.
2. Fisher KA, Nguyen N, Fouayzi H, Crawford S, **Singh S**, Dong M, Wittenberg R, Mazor KM. From COVID-19 Vaccine Hesitancy to Vaccine Acceptance: Results of a Longitudinal Survey. Public Health Rep. 2023 May 27:333549231176006. doi: 10.1177/00333549231176006. Epub ahead of print. PMID: 37243439.
3. Reis G, Dos Santos Moreira Silva EA, Medeiros Silva DC, Thabane L, de Souza Campos VH, Ferreira TS, Quirino Dos Santos CV, Ribeiro Nogueira AM, Figueiredo Guimaraes Almeida AP, Cançado Monteiro Savassi L, de Figueiredo Neto AD, Bitarães C, Cruz Milagres A, Diniz Callegari E, Campos Simplicio MI, Barra Ribeiro L, Oliveira R, Harari O, Wilson LA, Forrest JI, Ruton H, Sprague S, McKay P, Guo CM, Guyatt GH, Rayner CR, Boulware DR, Ezer N, Lee TC, McDonald EG, Bafadhel M, Butler C, Rodrigues Silva J, Dybul M, Mills EJ; **TOGETHER Investigators**; Oral Fluvoxamine With Inhaled Budesonide for Treatment of Early-Onset COVID-19 : A Randomized Platform Trial. *Ann Intern Med* 2023 May;176(5):667-675. PMID: 37068273; PMCID: PMC10111398.
4. Reis G, Moreira Silva EAS, Medeiros Silva DC, Thabane L, Campos VHS, Ferreira TS, Santos CVQ, Nogueira AMR, Almeida APFG, Savassi LCM, Figueiredo-Neto AD, Dias ACF, Freire Júnior AM, Bitarães C, Milagres AC, Callegari ED, Simplicio MIC, Ribeiro LB, Oliveira R, Harari O, Wilson LA,

Forrest JI, Ruton H, Sprague S, McKay P, Guo CM, Limbrick-Oldfield EH, Kanters S, Guyatt GH, Rayner CR, Kandel C, Biondi MJ, Kozak R, Hansen B, Zahoor MA, Arora P, Hislop C, Choong I, Feld JJ, Mills EJ, Glenn JS; **TOGETHER Investigators**. Early Treatment with Pegylated Interferon Lambda for Covid-19. *N Engl J Med* 2023 Feb 9;388(6):518-528

5. **Singh S**, ** Beyrer J, Zhou X, Swerdel J, Harvey RA, Hornbuckle K, Russo L, Ghauri K, Abi-Elias IH, Cox JS, Rodriguez-Watson C. Development and Evaluation of the Algorithm CErtaInty Tool (ACE-IT) to Assess Electronic Medical Record and Claims-based Algorithms' Fit for Purpose for Safety Outcomes. *Drug Saf* 2023 Jan;46(1):87-97.

6. Akenroye A, * Zhou G, Jackson JW, Segal J, Alexander GC, **Singh S**. Incidence of adverse events prompting switching between biologics among adults with asthma: A retrospective cohort study. *Allergy* 2023 Apr;78(4):1116-111

7. Fisher KA, Nguyen N, Fouayzi H, **Singh S**, Crawford S, Mazor KM. Impact of a Physician Recommendation on COVID-19 Vaccination Intent Among Vaccine Hesitant Individuals. *Patient Educ Couns 2023 Jan;106:107-112.*

8. Antonelli MT, Cox JS, Saphirak C, Gurwitz JH, **Singh S**, Mazor KM. Motivating deprescribing conversations for patients with Alzheimer's disease and related dementias: a descriptive study. *Ther Adv Drug Saf* 2022 Aug 23;13:20420986221118143. doi: 10.1177/20420986221118143.

9. Reis G, Silva EASM, Silva DCM, Thabane L, Milagres AC, Ferreira TS, Dos Santos CVQ, Campos VHS, Nogueira AMR, de Almeida APFG, Callegari ED, Neto ADF, Savassi LCM, Simplicio MIC, Ribeiro LB, Oliveira R, Harari O, Forrest JI, Ruton H, Sprague S, McKay P, Guo CM, Rowland-Yeo K, Guyatt GH, Boulware DR, Rayner CR, Mills EJ; **TOGETHER Investigators**. Effect of Early Treatment with Ivermectin among Patients with Covid-19. *N Engl J Med*. 2022 May 5;386(18):1721-1731.

10. Thorlund K, Sheldrick K, Meyerowitz-Katz G, **Singh**, Hill A. Making Statistical Sense of the Molnupiravir MOVE-OUT Clinical Trial. *Am. J. Trop. Med*. Hyg., 2022, pp. 1–4 doi:10.4269/ajtmh.21-1339

11. Fisher KA, Nguyen N, Crawford S, Fouayzi H, **Singh S**, Mazor KM. Preferences for COVID-19 vaccination information and location: Associations with vaccine hesitancy, race and ethnicity, *Vaccine* 2021, https://doi.org/10.1016/j.vaccine.2021.09.058.

12. McGarvey L, Rubin BK, Ebihara S, Hegland K, Rivet A, Irwin RS, Bolser DC, Chang AB, Gibson PG, Mazzone SB; **CHEST Expert Cough Panel**. Global Physiology and Pathophysiology of Cough: Part 2. Demographic and Clinical Considerations: CHEST Expert Panel Report. *Chest 2021* Apr 24:S0012-3692(21)00764-9. doi: 10.1016/j.chest.2021.04.039. Epub ahead of print. PMID: 33905678.

13. Chang HY, Chou YY, Tang W, Chang GM, Hsieh CF, **Singh S**, Tung YC. Association of antidiabetic therapies with lower extremity amputation, mortality, and healthcare cost from a nationwide retrospective cohort study in Taiwan. *Sci Rep* 2021 Mar 26;11(1):7000. doi: 10.1038/s41598-021-86516-4. PMID: 33772082.

14. **Singh S**, Cocoros NM, Haynes K, Nair VP, Harkins TP, Rochon PA, Platt R, Dashevsky I, Reynolds J, Mazor KM, Bloomstone S, Anzuoni K, Crawford SL, Gurwitz JH. Identifying Prescribing Cascades in Alzheimer's Disease and Related Dementias: The Calcium Channel Blocker-Diuretic Prescribing Cascade. Pharmacoepidemiol Drug Saf. 2021 Mar 14. doi: 10.1002/pds.5230. Epub ahead of print. PMID: 33715299.

15. Gurwitz JH, Kapoor A, Garber L, Mazor KM, Wagner J, Cutrona SL, **Singh S**, Kanaan AO, Donovan JL, Crawford S, Anzuoni K, Konola TJ, Zhou Y, Field TS. Effect of a Multifaceted Clinical Pharmacist Intervention on Medication Safety After Hospitalization in Persons Prescribed High-risk Medications: A Randomized Clinical Trial. JAMA Intern Med. 2021 Mar 1. doi: 10.1001/jamainternmed.2020.9285. Epub ahead of print. PMID: 33646267.

16. Lee KK, Davenport PW, Smith JA, Irwin RS, McGarvey L, Mazzone SB, Birring SS; **CHEST Expert Cough Panel**. Global Physiology and Pathophysiology of Cough: Part 1: Cough Phenomenology - CHEST Guideline and Expert Panel Report. Chest. 2021 Jan;159(1):282-293. doi: 10.1016/j.chest.2020.08.2086. Epub 2020 Sep 2. PMID: 32888932.

17. Irwin RS, Dudiki N, French CL; **CHEST Expert Cough Panel**. Life-Threatening and Non-Life-Threatening Complications Associated With Coughing: A Scoping Review. Chest. 2020 Nov;158(5):2058-2073. doi: 10.1016/j.chest.2020.06.012. Epub 2020 Jun 19. PMID: 32565267.

18. Chang AB, Oppenheimer JJ, Irwin RS; **CHEST Expert Cough Panel**. Managing Chronic Cough as a Symptom in Children and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2020 Jul;158(1):303-329. doi: 10.1016/j.chest.2020.01.042. Epub 2020 Mar 14. PMID: 32179109.

19. **Singh S**, Cocoros NM, Haynes K, Nair VP, Harkins TP, Rochon PA, Platt R, Dashevsky I, Reynolds J, Mazor KM, Bloomstone S, Anzuoni K, Crawford SL, Gurwitz JH. Antidopaminergic-Antiparkinsonian Medication Prescribing Cascade in Persons with Alzheimer's Disease. *J Am Geriatr Soc* 2021 Jan 11. doi: 10.1111/jgs.17013. Online ahead of print.

20. Bloomstone S, Cocoros N, Gurwitz J, Haynes K, Nair V, Platt R, Rochon P, **Singh S**, Mazor KM. Prescribing Cascades in Patients with Alzheimer's Disease: Engaging Patients, Caregivers, Payers, and Providers in a Qualitative Evaluation of Print Educational Materials. *Therapeutic Advances Drug Safety. First published October 30, 2020. https://journals.sagepub.com/doi/10.1177/2042098620968310*

21. *Fukunaga MI, Halligan K, Kodela J, Toomey S, Furtado V, Luckmann R, Han PKJ, Mazor KM, **Singh S**. **Tools to promote shared decision making in lung cancer screening using low-dose computerized tomography: a systematic review [published online ahead of print, 2020 Jul 3]. *Chest*. 2020; Dec;158(6):2646-2657

22. Heyward J, Mansour O, Olson L, ****Singh S**, Alexander GC; Association Between Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors and Lower Extremity Amputation: A Systematic Review and Meta-Analysis. *PloS One* 2020 Jun 5;15(6):e0234065. doi: 10.1371/journal.pone.0234065

23. Malesker MA, Callahan-Lyon P, Madison JM, Ireland B, Irwin RS; **CHEST Expert Cough Panel**. Chronic Cough Due to Stable Chronic Bronchitis: CHEST Expert Panel Report [published online ahead of print, 2020 Feb 24]. *Chest* 2020;S0012-3692(20)30324-X. doi:10.1016/j.chest.2020.02.015

24. Smith MP, Lown M, **Singh S**, Ireland B, Hill AT, Irwin RS on behalf of the **CHEST Expert Cough Panel**: Chest Guideline and Expert Panel Report. Immunocompetent Adult Outpatients with Cough Due to Acute Bronchitis: CHEST Expert Panel Report.[published online ahead of print, 2020 Feb 21]. *Chest* 2020;S0012-3692(20)30329-9. doi:10.1016/j.chest.2020.01.044

25. Côté A, Russell RJ, Boulet LP, et al. Managing Chronic Cough due to Asthma and NAEB in Adults and Adolescents. **CHEST Expert Cough Panel** Report [published online ahead of print, 2020 Jan 20]. *Chest* 2020;S0012-3692(20)30045-3. doi:10.1016/j.chest.2019.12.021

26. Epstein MM, Saphirak C, Zhou Y, LeBlanc C, Rosmarin AG, Ash A, **Singh S**, Fisher K, Birmann BM, Gurwitz J. Identifying Monoclonal Gammopathy of Undetermined Significance in Electronic Health Data. *Pharmacoepidemiol Drug Saf* 2019 Nov 17[Online ahead of print] PMID: 31736189 DOI: 10.1002/pds.4912

27. Min JY, Grijalva CG, Morrow JA, Whitmore CC, Hawley RE, **Singh S**, Swain RS, Griffin MR. A Comparison of Two Algorithms to Identify Sudden Cardiac Deaths in Computerized Database. *Pharmacoepidemiol Drug Saf*. 2019 Aug 7. doi: 10.1002/pds.4845. [Epub ahead of print]

28. ****Singh S**, Mazor KM, Fisher K. Positive deviance approaches to improving vaccination coverage rates within health care systems: a systematic review. *J Comp Eff Res*. 2019 Oct;8(13):1055-1065.

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Correspondence

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Major curricular offerings

2 credit Course in comparative effectiveness research for the Johns Hopkins ICTR 2015-2016

Biography

Sonal Singh MD, MPH, FACP received his MD from Patna Medical College India (1998) and completed his internal medicine residency training at Unity Health System, affiliate of Strong Memorial Hospital Rochester, NY. He is a Diplomate of the ABIM and a Fellow of the American College of Physicians. He obtained an MPH from Johns Hopkins Bloomberg School of Public Health (2008) and completed research training at the Johns Hopkins Hospital as a Junior Faculty Research Scholar supported by the NIH. He has taught and held faculty appointments at Wake Forest University School of Medicine and Johns Hopkins University School of Medicine and Public Health. He was the Associate Director for the Center for Drug Safety and Effectiveness and core faculty Evidence Based Practice Center and the Center for Public Health and Human Rights at Johns Hopkins University. He has received the Tinsley R Harrison Teaching Award for Education at Wake Forest University, Mid-Atlantic Society of General Internal Medicine Clinician Investigator of the Year Award, the Bruce P Squires Award for the best research paper of the year from the Canadian Medical Association Journal. His research has been published in leading medical journals such as the New England Journal of Medicine, Journal of the American Medical Association, British Medical Journal and The Lancet. These have been

featured in Nature Medicine, NYTIMES, CNN, Washington Post, and the WSJ. His work has been supported by the National Institute of Health, Food and Drug Administration, Agency for HealthCare Research and Quality, Patient Centered Outcomes Research Institute, the World Health Organization International Agency for Research on Cancer and the World Bank. He is a practicing general internist with a passion for managing patients with complex medical conditions.

Research and Clinical Interests

Dr. Singh is an internal medical specialist and epidemiologist specializing in assessing the safety of medications. He conducts clinical research with a focus on evidence synthesis, pharmacoepidemiology and shared decision making. He has led and participated in many impactful studies which have been incorporated into national and international guidelines on the treatment of chronic conditions. His research focusses on improving the safe use of medications for patients with chronic conditions. He has also led several efforts to improve the methodologic quality of studies that assess the safety and effectiveness of medications. He has also contributed to studies of developing new tools for measurement of human rights violations.

Personal Statement

I believe in making shared decisions about treatment after discussing patient's preferences and preferences. I believe that effective and safe treatments should improve quality of life and clinical outcomes along with any laboratory markers of disease. I try to understand patients' perspective on treatment. I deliver care in partnership with a highly collaborative and competent group of physicians, nurses, and staff at UMass Chan Medical School where we offer the best options for our patients.

EXHIBIT B

Trial Testimony

I have not provided trial testimony.

Depositions (last four years)

1. *Coates v. United States*, 3:18-cv-314 (W.D. Ky.): I have provided expert report and deposition on behalf of the plaintiff on July 16, 2020.
2. *In re: Tasigna (Nilotinib) Products Liability Litigation*, MDL No. 3006 (U.S. District Court for the Middle District of Florida): I have provided expert report and deposition on February 2, 2023 on behalf of the plaintiff.
3. *Van Foutch and Mary Foutch v. Jonathan Wilks MD and OU Medical Center*, Case No. CJ-2021-2934 (District Court of Oklahoma City): I have provided deposition on behalf of the defendants on the medicolegal standard of care for treatment of Rocky Mountain Spotted fever.